TRIEMTA TABLETS
PM02832301

SCHEDULING STATUS:
S4

PROPRIETARY NAME (AND DOSAGE FORM):
TRIEMTA TABLETS (Film-coated Tablets)

COMPOSITION:
Each film-coated tablet contains efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg. Sugar free.
Other ingredients include microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, magnesium stearate (vegetable grade), pregelatinised starch, polyvinyl alcohol, titanium dioxide (C.I. No. 77891), polyethylene glycol, talc, red iron oxide (C.I. No. 77491), black iron oxide (C.I. No. 77499).

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

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
TRIEMTA TABLETS is a fixed dose combination tablet containing efavirenz, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF). Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI); emtricitabine is a synthetic nucleoside analogue of cytidine and tenofovir DF is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analogue of adenosine 5' monophosphate.
Efavirenz:
Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Efavirenz does not inhibit HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ.
Emtricitabine:
Emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI), is a synthetic nucleoside analogue of cytidine. Cellular enzymes phosphorylate emtricitabine to emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate competes with the natural substrate, deoxycytidine 5'-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 EC90 value) emerged rapidly under selection *in vitro*. Genotypic characterisation of these viruses identified mutations resulting in single amino acid substitutions L100I or V179D, double substitutions L100I/V108I, and triple substitutions L100I/V179D/Y181C in RT.
Emtricitabine:
HIV isolates resistant to emtricitabine have been selected *in vitro*. Genotypic analysis of these isolates demonstrated that reduced emtricitabine susceptibility was associated with a mutation in the HIV RT gene at codon 184. This mutation caused an amino acid substitution of methionine by valine or isoleucine (M184V/I).
Tenofovir disoproxil fumarate:
Isolates of HIV-1 that exhibited reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and demonstrated a reduced susceptibility to tenofovir of between 2- and 4-fold.
Cross-resistance:
Efavirenz, emtricitabine and tenofovir disoproxil fumarate:
Cross-resistance has been recognised among NNRTIs. It is also known that cross-resistance may develop among certain NRTIs. The M184V/I and/or K65R substitutions selected *in vitro* by the combination of emtricitabine and tenofovir are also seen in some HIV-1 strains isolated from individuals failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Cross-resistance among these medicines may therefore develop in patients whose virus harbours either or both of these amino acid substitutions.

Pharmacokinetic properties:
Efavirenz:
Absorption:
Peak efavirenz plasma concentrations of 1,6 – 9,1 μM are reached by 5 hours following single oral doses of 100 mg to 1600 mg given to uninfected volunteers. Although dose-related increases in C_{max} and AUC are seen for doses up to 1600 mg, these increases are less than proportional, indicating diminished absorption at higher doses. Steady state plasma concentrations are reached in 6 to 10 days.
Distribution:
Efavirenz is highly plasma protein bound (approximately 99,5 – 99,75 %) and predominantly to albumin. Cerebrospinal fluid concentrations ranged from 0,26 to 1,19 % (mean 0,69 %) of the corresponding plasma concentrations in HIV-1 infected individuals administered 200 to 600 mg efavirenz once daily for at least one month. This is about three times higher than the non-protein-bound (free) fraction of efavirenz in plasma.
Metabolism:
Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. The metabolites are not active against HIV-1. CYP3A4 and CYP2B6 are the major isozymes involved in efavirenz metabolism. Efavirenz, through induction of P450 enzymes, induces its own metabolism.
Elimination:
Efavirenz has a long terminal half-life of 52 – 76 hours and 40 – 55 hours after single and multiple doses, respectively. Subsequent to the administration of a radio-labelled dose, 14 – 34 % of efavirenz is recovered in the urine (mostly as metabolites) and 16 – 61 % is recovered in the faeces (mostly as parent medicine).

Emtricitabine:
The pharmacokinetic properties of emtricitabine are summarised in Table 1.
Absorption: Following oral administration of emtricitabine (200 mg), emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 – 2 hours post-dose.
Distribution: In vitro binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 – 200 μg/mℓ.
Metabolism and elimination: Following administration of radio-labelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine (200 mg), the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate:
The pharmacokinetic properties of tenofovir disoproxil fumarate are summarised in Table 1.
Absorption: Following oral administration of tenofovir, maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hour.
Distribution: *In vitro* binding of tenofovir to human plasma proteins < 0,7 % is independent of concentration over the range of 0,01 – 25 μg/mℓ.
Metabolism and elimination: Approximately 70 – 80 % of the intravenous dose of tenofovir is recovered as unchanged in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours.

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

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

[1] NC = Not calculated
[2] Median (range)
[3] Mean (± SD)
[4] Data presented as steady state values.

Effects of food on oral absorption:
TRIEMTA 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. **TRIEMTA TABLETS** is not recommended for paediatric administration. Pharmacokinetics of efavirenz, emtricitabine, and tenofovir have not been fully evaluated in the elderly (more than 65 years) (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Patients with impaired renal function
Efavirenz: The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1 % of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.
Emtricitabine and tenofovir disoproxil fumarate: The pharmacokinetics of emtricitabine and tenofovir DF are altered in patients with renal impairment. In patients with creatinine clearance less than 50 mℓ/min, C_{max} and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased (see **CONTRAINDICATIONS, WARNINGS AND SPECIAL PRECAUTIONS, Renal impairment**).

Patients with hepatic impairment
Efavirenz: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see **WARNINGS AND 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:
TRIEMTA TABLETS is indicated as mono- or combination therapy with other anti-retroviral medicines for HIV-1 infection in adults.

CONTRAINDICATIONS:
TRIEMTA TABLETS is contraindicated in patients:
- With previously demonstrated hypersensitivity to efavirenz, emtricitabine or tenofovir or to any of the other components of **TRIEMTA TABLETS**.
- Severe hepatic impairment (Child Pugh Class C).
- A history of previous liver injury/failure with efavirenz containing antiretroviral treatment (ART).
- With moderate to severe impairment of renal function (creatine clearance < 50 mℓ) (see **WARNINGS AND SPECIAL PRECAUTIONS** and **DOSAGE AND DIRECTIONS FOR USE**).
- Who are concurrently receiving treatment with cisapride, midazolam, triazolam, pimozide, bepridil or ergot alkaloids (for example ergotamine, dihydroergotamine, ergonovine and methylergonovine), because competition for CYP3A4 by the efavirenz in **TRIEMTA TABLETS** could result in inhibition of the metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g., cardiac dysrhythmias, prolonged sedation or respiratory depression).
- Who are concurrently using voriconazole, since efavirenz significantly decreases voriconazole plasma concentrations, while voriconazole significantly increases efavirenz plasma concentrations. (See **INTERACTIONS**). Since **TRIEMTA TABLETS** is a fixed-dose combination medicine, the dose of efavirenz cannot be altered; therefore voriconazole and **TRIEMTA TABLETS** must not be co-administered.
- Who are pregnant or breastfeeding (see **PREGNANCY AND LACTATION**).
- Who are concurrently using St. John's Wort (*Hypericum perforatum*) or St. John's Wort containing medicines (see **INTERACTIONS**).
- **TRIEMTA TABLETS** is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

WARNINGS AND SPECIAL PRECAUTIONS:

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

Lactic acidosis / hyperlactataemia:
Use of **TRIEMTA TABLETS** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.
Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.
In patients with suspicious symptoms, measure the venous lactate level (normal < 2 mmol/l) and the serum bicarbonate and respond as follows:
– **Lactate 2 – 5 mmol/l with minimum symptoms:** switch to medicines that are less likely to cause lactic acidosis.
– **Lactate 5 – 10 mmol/l with symptoms and or with reduced bicarbonate:** Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism).
– **Lactate > 10 mmol/l: STOP all therapy** (80 % mortality).
The above lactate values may not be applicable to paediatric patients.
Caution should be exercised when administering **TRIEMTA TABLETS** to patients with known factors for liver disease.
Treatment with **TRIEMTA TABLETS** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatoxicity.

Mitochondrial dysfunction:
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms.

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

Liver disease:
Use of **TRIEMTA TABLETS** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **TRIEMTA TABLETS** has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines.
Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

There is some evidence that efavirenz is associated with three clinical pathological patterns of drug induced liver failure in HIV positive patients of which the sub massive necrosis histological pattern seems to be associated with a high morbidity/mortality risk and may present many months after therapy has been initiated or even stopped. Risk factors include younger age, CD4+ counts ≥ 350 cells/μl and female gender.

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

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

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

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

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

Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.
Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).
In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines.
In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.
Discontinuation of **TRIEMTA TABLETS** therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis.

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

St. John's Wort:
Concomitant use of **TRIEMTA TABLETS** and St. John's Wort (*Hypericum perforatum*) or St. John's Wort containing products is contraindicated. Co-administration of NNRTIs, including efavirenz with St. John's Wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

Psychiatric symptoms:
Serious psychiatric adverse events have been reported in patients treated with efavirenz. These side effects include: severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behaviour, paranoid reactions and manic reactions. Treatment with efavirenz is associated with an increase in the occurrence of these psychiatric symptoms.
There have also been post marketing reports of death by suicide, delusions, and psychosis-like behaviour; a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, therefore **TRIEMTA TABLETS.**

Nervous system and psychiatric symptoms:
These symptoms included dizziness, insomnia, impaired concentration, somnolence, abnormal dreams and hallucinations. Other reported symptoms are euphoria, confusion, agitation, amnesia, stupor, abnormal thinking, and depersonalisation. These symptoms usually begin during the first or second day of therapy and may resolve after the first 2 - 4 weeks of therapy. Patients should be informed that these common symptoms may improve with continued therapy and may not be predictive of subsequent onset of the less frequent psychiatric symptoms. Dosing at bedtime may improve the tolerability of these nervous system symptoms.
Patients receiving **TRIEMTA TABLETS** should be alerted to the potential for additive central nervous system effects when **TRIEMTA TABLETS** is used concomitantly with alcohol or psychoactive medicines.

Renal impairment:
Emtricitabine and tenofovir, two of the active ingredients in **TRIEMTA TABLETS**, are principally eliminated by the kidney. **TRIEMTA TABLETS** should not be administered to patients with creatinine clearance < 50 mℓ/min (see **Contraindications**).
There have been reports of renal impairment including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia) in association with the use of tenofovir DF (see **Side Effects**).
It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with **TRIEMTA TABLETS** (see **Dosage and Directions for Use**). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.
The use of **TRIEMTA TABLETS** should be avoided in patients who are concurrently taking or who have recently taken a nephrotoxic medicine.

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

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

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

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

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

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

Immune Reconstitution Inflammatory Syndrome:
Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically it presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections:
Patients receiving **TRIEMTA TABLETS** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:
Patients should be advised that current antiretroviral therapy, including **TRIEMTA TABLETS**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

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

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

Effects on the ability to drive and use machines:
TRIEMTA TABLETS may lead to dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that, if they develop these symptoms, they should keep away from potentially hazardous tasks, such as driving or operating machinery.

INTERACTIONS:
Efavirenz: Efavirenz has been shown *in vivo* to induce CYP3A4 and CYP2B6. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9 and 2C19 isozymes in the range of observed efavirenz plasma concentrations. Co-administration of efavirenz with medicines primarily metabolised by these isozymes may result in altered plasma concentrations of the co-administered medicine. Therefore, appropriate dose adjustments may be necessary for these medicines.
Medicines that induce CYP3A4 activity (e.g., phenobarbitone, rifampicin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Efavirenz exposure may be increased by medicines (such as ritonavir) or grapefruit juice which inhibit CYP3A4 or CYP2B6 activity.
Emtricitabine and tenofovir disoproxil fumarate: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of **TRIEMTA TABLETS** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated medicines. Some examples include, but are not limited to aciclovir, adefovir dipivoxil, cidofovir, ganciclovir, valaciclovir, and valganciclovir, aminoglycosides, amphotericin B, foscarnet, pentamidine and interleukin-2.
Co-administration of tenofovir DF and didanosine should be undertaken with 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. **TRIEMTA 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 **TRIEMTA TABLETS** is summarised in Table 2 and 3. The medicine interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual medicines or are potential medicine interactions; no medicine interaction studies have been conducted using the combination of actives such as in **TRIEMTA TABLETS**. The tables include potentially significant interactions, but are not all inclusive.

Table: 2
Medicines that are contraindicated or not recommended for use with TRIEMTA TABLETS

Medicine Class: Medicine Name	Clinical Comment
Antifungal: voriconazole	CONTRAINDICATED because efavirenz significantly decreases voriconazole plasma concentrations and co-administration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects.
Anti-migraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/ or life threatening reactions such as acute ergot toxicity characterised by peripheral vasospasm and ischaemia of the extremities and other tissues.
Anti-retroviral: efavirenz, emtricitabine, tenofovir DF, lamivudine	Not for use with **TRIEMTA TABLETS** because the active ingredients- emtricitabine, tenofovir DF, emtricitabine/ tenofovir DF and efavirenz are components of **TRIEMTA TABLETS**. Lamivudine is similar to emtricitabine.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
Calcium channel blocker: bepridil	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
GI motility medicine: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac dysrhythmias.
St. John's Wort *(Hypericum perforatum)*	CONTRAINDICATED: Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz.

Table: 3
Established and Other Potentially Significant 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 medicines		
Protease inhibitor: Amprenavir	↓ amprenavir concentration	Efavirenz has the potential to decrease serum concentrations of amprenavir.
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and **TRIEMTA 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 **TRIEMTA TABLETS** is administered with fosamprenavir once daily. No change in the ritonavir dose is required when **TRIEMTA TABLETS** is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when **TRIEMTA 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 **TRIEMTA TABLETS**. Therefore co-administration of **TRIEMTA 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. TRIEMTA 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 **TRIEMTA TABLETS** is used in combination with ritonavir.
Protease Inhibitor: Saquinavir	↑ saquinavir concentration	Should not be used as sole protease inhibitor in combination with **TRIEMTA 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 TRIEMTA TABLETS. Data are not available to recommend a dose adjustment of didanosine for patients weighing less than 60 kg.** When co-administered, **TRIEMTA 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 **TRIEMTA TABLETS** should be under fasted conditions. **Co-administration of TRIEMTA TABLETS and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events.**
Other medicines		
Anticoagulant: Warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for **TRIEMTA TABLETS**. Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbitone	↓ anticonvulsant concentration ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Valproic acid/Efavirenz	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.	**TRIEMTA TABLETS** and valproic acid can be co-administered without dose adjustment. Patients should be monitored for seizure control.
Vigabatrin/Efavirenz Gabapentin/Efavirenz	Interaction not studied. Clinically significant interactions are not expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and are unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz	**TRIEMTA TABLETS** and vigabatrin or gabapentin can be co-administered without dose adjustment.
Antidepressant : Sertraline.	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Paroxetine/Efavirenz	Paroxetine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	**TRIEMTA TABLETS** and paroxetine can be co-administered without dosage adjustment.
Fluoxetine/Efavirenz	Interaction not studied. Since fluoxetine shares a similar metabolic profile with paroxetine, i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine	**TRIEMTA TABLETS** and fluoxetine can be co-administered without dosage adjustment.
Antifungals: Itraconazole	↓ itraconazole concentration ↓ hydroxy-itraconazole concentration	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Posaconazole	↓ posaconazole	Concomitant use should be avoided.
Ketoconazole	↓ ketoconazole concentration	Medicine interaction studies with **TRIEMTA 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 **TRIEMTA 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 **TRIEMTA TABLETS** .
Antimycobacterial: Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50 %. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimycobacterial: Rifampicin	↓ efavirenz concentration	Clinical significance of reduced Efavirenz concentration is unknown. Dosing recommendations for concomitant use of **TRIEMTA 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 **TRIEMTA TABLETS** is necessary when administered with diltiazem.
Others (e.g., felodipine, nifedipine, nicardipine, verapamil)	↓ N-monodesmethyl diltiazem concentration ↓ calcium channel blocker.	No data are available on potential interactions of efavirenz with other calcium channel blockers that are substrates of CYP3A4 enzymes. The potential exists for reduction in plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response.
HMG-CoA reductase inhibitors: Atorvastatin, Pravastatin, Simvastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin concentration	Plasma concentrations of atorvastatin pravastatin and simvastatin decreased with efavirenz. Consult the full package inserts for the HMG-CoA reductase inhibitor for guidance on individualising the dose.
Narcotic analgesic: Methadone	↓ methadone concentration	Co-administration of efavirenz in HIV-1 infected individuals with a history of injection medicine use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Oral contraceptives: Ethinyl oestradiol	↑ ethinyl oestradiol concentration	Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterised. A reliable method of barrier contraception should be used in addition to oral contraceptives.
Artemether/Lumefantrine /Efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg daily.)	Artemether: AUC: ↓ 51 % C_{max}: ↓ 21 % Dihydroartemisinin (active metabolite): AUC: ↓ 46 % C_{max}: ↓ 38 % Lumefantrine: AUC: ↓ 21 % C_{max}: ↔ Efavirenz: AUC: ↓ 17 % C_{max}: ↔ (CYP3A4 induction)	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when **TRIEMTA TABLETS** and artemether/lumefantrine tablets are co-administered.
Atovaquone and proguanil hydrochloride/Efavirenz (250/100 mg single dose/600 mg daily.)	Atovaquone: AUC: ↓ 75 % (↓ 62 to ↓ 84) C_{max}: ↓ 44 % (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43 % (↓ 7 to ↓ 65) C_{max}: ↔	Concomitant administration of atovaquone/proguanil with **TRIEMTA TABLETS** should be avoided whenever possible.

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:
Interaction studies were performed with efavirenz and other medicines likely to be co-administered or medicines commonly used as probes for pharmacokinetic interaction. There was no clinically significant interaction observed between efavirenz and zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine or paroxetine. Single doses of famotidine or an aluminium and magnesium antacid with simethicone had no effects on efavirenz exposures.
Emtricitabine and tenofovir disoproxil fumarate:
No clinically significant medicine interactions have been observed between emtricitabine and tenofovir, indinavir, stavudine, tenofovir DF and zidovudine. Similarly no clinically significant interactions have been observed between tenofovir DF and abacavir, adefovir dipivoxil, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin and saquinavir/ ritonavir in studies conducted in healthy volunteers.
Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy, oral contraceptives or single dose of ribavirin, steady-state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating a lack of clinically significant medicine interaction between these medicines and tenofovir DF.

PREGNANCY AND LACTATION:
Pregnancy:
TRIEMTA TABLETS should not be used during pregnancy.
Efavirenz: There have been reports of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to efavirenz-containing regimens in the first trimester. As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes are sealed), this potential risk would concern women exposed to efavirenz during the first trimester of pregnancy.
Malformations have been observed in foetuses from efavirenz-treated monkeys.
Barrier contraception should always be employed in combination with other contraceptive methods (e.g., oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of **TRIEMTA TABLETS** is recommended.
Women of childbearing potential should undergo pregnancy testing prior to initiation of treatment with **TRIEMTA TABLETS**.

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

DOSAGE AND DIRECTIONS FOR USE:
Adults:
The recommended dose of **TRIEMTA TABLETS** is one tablet taken orally once daily.
TRIEMTA TABLETS should be taken on an empty stomach, since food may increase efavirenz exposure and this may cause an increase in the frequency of adverse reactions. In order to improve the tolerability to efavirenz with respect to undesirable effects on the nervous system, it is recommended that **TRIEMTA TABLETS** be taken at bedtime.
Children and adolescents:
TRIEMTA TABLETS is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.
Renal impairment:
TRIEMTA TABLETS is not recommended for patients with moderate to severe impairment of renal function (creatinine clearance < 50 mℓ/min). (see Contraindications).
Where discontinuation of treatment with one of the components of **TRIEMTA TABLETS** is indicated or where dose modification is required, separate preparations of efavirenz, emtricitabine and tenofovir are available. Please refer to the individual package inserts of these medicines.

SIDE EFFECTS
EFAVIRENZ
Immune system disorders
Less frequent: Hypersensitivity.
Frequency not known: Immuno-allergic liver injury/failure.
Metabolism and nutrition disorders
Frequent: Weight gain, hypertriglyceridemia.
Less frequent: Hypercholesterolaemia.
Frequency not known: Weight loss, redistribution/accumulation of body fat.
Psychiatric disorders
Frequent: Depression, anxiety, abnormal dreams, insomnia.
Less frequent: Stupor, confusion, impaired concentration, abnormal thinking, agitation, amnesia, delirium, emotional lability, euphoria, hallucination, psychosis, suicide attempt, suicide ideation, completed suicide, paranoia, mania, delusion, neurosis.
Frequency not known: Inappropriate behaviour, apathy.
Nervous system disorders
Frequent: Dizziness, headache, somnolence, cerebellar coordination and balance disturbance, disturbance in attention.
Less frequent: Abnormal coordination, ataxia, convulsions, migraine headaches, neuralgia, paraesthesia, peripheral neuropathy, speech disorder, tremor, hypoaesthesia, amnesia, thinking abnormal, agitation.
Eye disorders
Less frequent: Abnormal vision, blurred vision.
Ear and labyrinth disorders
Less frequent: Tinnitus, vertigo.
Cardiac disorders
Less frequent: Palpitations and tachycardia.
Vascular disorders
Less frequent: Flushing.
Respiratory, thoracic and mediastinal disorders
Less frequent: Asthma, upper respiratory tract infections, sinusitis.
Frequency not known: Dyspnoea.
Gastrointestinal disorders
Frequent: Nausea, vomiting, diarrhoea, abdominal pain.
Less frequent: Gastritis, gastroenteritis, gastro-oesophageal reflux, increased appetite, taste perversion, pancreatitis.
Frequency not known: Constipation, malabsorption.
Hepato-biliary disorders
Frequent: Elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated gamma-glutamyltransferase (GGT).
Less frequent: Hepatitis, hepatic failure.
Skin and subcutaneous tissue disorders
Frequent: Diffuse maculopapular rash, pruritus.
Less frequent: Severe rash associated with blistering, moist desquamation or ulceration, acne, alopecia, eczema, folliculitis, seborrhoea, skin exfoliation, urticaria, erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome.
Frequency not known: Nail disorders, skin discolouration.
Musculoskeletal, connective tissue and bone disorders
Less frequent: Arthralgia, myalgia.
Frequency not known: Myopathy.
Reproductive system and breast disorders
Less frequent: Impotence, decreased libido, increased libido, gynaecomastia.
General disorders and administrative site conditions
Frequent: Fatigue.
Less frequent: Asthenia, malaise, pain, syncope, influenza-like symptoms, alcohol intolerance, hot flushes.

EMTRICITABINE:
Blood and lymphatic system disorders
Frequent: Neutropenia.
Less frequent: Anaemia.
Immune system disorders
Frequent: Allergic reaction.
Metabolism and nutrition disorders
Frequent: Hyperglycaemia, hypertriglyceridaemia.
Frequency not known: Lactic acidosis, usually associated with severe hepatomegaly and steatosis.
Psychiatric disorders
Frequent: Sleep disturbances (abnormal dreams, insomnia).
Frequency not known: Depressive disorder.
Nervous system disorders
Frequent: Headache, dizziness.
Frequency not known: Asthenia, neuropathy, peripheral neuritis, paraesthesia.
Gastrointestinal disorders
Frequent: Nausea, vomiting, diarrhoea, elevated amylase including elevated pancreatic amylase, elevated serum lipase, abdominal pain, dyspepsia.
Hepatobiliary disorders
Frequent: Elevated serum AST and /or elevated serum ALT, hyperbilirubinaemia.
Skin and subcutaneous tissue disorders
Frequent: Rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction), skin discolouration, manifested by hyperpigmentation on the palm and/or soles.
Less frequent: Angioedema.
Musculoskeletal and connective tissue disorders
Frequent: Elevated creatine kinase.
Frequency not known: Arthralgia, myalgia.
Respiratory, thoracic and mediastinal disorders
Frequency not known: Increased cough and rhinitis.
General disorders and administration site conditions
Frequent: Pain, asthenia.

TENOFOVIR
Blood and lymphatic system disorders
Frequency not known: Neutropenia, haematuria.
Immune system disorders
Frequency not known: Allergy, allergic reaction.
Metabolism and nutrition disorders
Frequent: Hypophosphataemia.
Less frequent: Hypokalaemia, lactic acidosis, usually associated with severe hepatomegaly and steatosis.
Frequency not known: Hypertriglyceridaemia, hyperglycaemia.
Psychiatric disorders
Frequency not known: Depression, anxiety.
Nervous system disorders
Frequent: Dizziness, headache.
Frequency not known: Peripheral neuropathy (including peripheral neuritis, neuropathy).
Respiratory, thoracic and mediastinal disorders
Frequency not known: Chest pain, pneumonia, dyspnoea.
Gastrointestinal disorders
Frequent: Nausea, vomiting, diarrhoea, abdominal pain, abdominal distension, flatulence, dyspepsia and anorexia.
Less frequent: Raised serum amylase concentration, pancreatitis.
Hepatobiliary disorders
Frequent: Increased transaminases.
Less frequent: Hepatic steatosis, hepatitis.
Skin and subcutaneous tissue disorders:
Frequent: Skin rashes (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash).
Less frequent: Angioedema.
Musculoskeletal and connective tissue disorders
Less frequent: Rhabdomyolysis, muscular weakness, osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy.
Frequency not known: Back pain, arthralgia, myalgia.
Renal and urinary disorders:
Less frequent: Proteinuria, proximal renal tubulopathy including Fanconi syndrome, renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.
Frequency not known: Renal impairment.
General disorders and administration site conditions:
Frequent: Asthenia.
Frequency not known: Fever, sweating, weight loss.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
In the event of overdose, the patient must be monitored for evidence of toxicity, and standard supportive treatment given as necessary.
Efavirenz:
Symptoms of overdose include increased nervous system symptoms and involuntary muscle contractions. Treatment of efavirenz overdose should consist of general supportive measures. These should include vital sign monitoring and observation of the patient's clinical status. Activated charcoal may be administered to aid removal of unabsorbed medicine. Dialysis is unlikely to significantly remove efavirenz from the blood, since the medicine is highly protein bound.
Emtricitabine:
Haemodialysis treatment removes approximately 30 % of the emtricitabine dose over a 3-hour dialysis period starting within 1,5 hours of emtricitabine dosing (blood flow rate of 400 mℓ/min and a dialysate flow rate of 600 mℓ/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.
Tenofovir disoproxil fumarate :
Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour haemodialysis session removes approximately 10 % of the administered tenofovir dose.

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

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

STORAGE INSTRUCTIONS:
Store at or below 25 °C. Protect from light and moisture.
Keep the HDPE containers closed.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
51/20.2.8/0121.120

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

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
29 September 2017

PATIENT INFORMATION LEAFLET

S4

SCHEDULING STATUS:

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

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

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

BEFORE YOU TAKE TRIEMTA TABLETS
Do not take TRIEMTA TABLETS:
- If you are hypersensitive (allergic) to efavirenz, emtricitabine and tenofovir disoproxil fumarate, or any of the other ingredients of **TRIEMTA TABLETS**.
- If you have kidney problems.
- If you have liver problems.
- If you had a liver disorder or liver failure attributed to treatment with **TRIEMTA TABLETS**.
- If you are pregnant or breastfeeding.
- If you are currently taking any of the following medicines:
  - cisapride (used to treat heartburn)
  - bepridil (used to treat heart disease)
  - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches)
  - midazolam or triazolam (used to help you sleep)
  - pimozide (used to treat certain mental conditions)
  - voriconazole (for fungal infections)
  - terfenadine (used to treat hay fever or other allergies)
  - St. John's Wort *(Hypericum perforatum)* (a herbal remedy used for depression and anxiety).
  - **If you are taking any of these medicines, tell your doctor immediately.** Taking these medicines with **TRIEMTA TABLETS** could cause serious or life-threatening side effects or stop these medicines from working properly.
  - The safety and effectiveness of **TRIEMTA TABLETS** in children and patients younger than 18 years has not been determined, therefore it should not be used in patients younger than 18 years.

Take special care with TRIEMTA TABLETS:
- **TRIEMTA TABLETS** may cause lactic acidosis, together with an enlarged liver, which can be fatal. Deep, rapid breathing, drowsiness, and symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. Lactic acidosis occurs more often in women. Patients who are overweight are more at risk.
- Tell your doctor if you have liver disease (including hepatitis B). Independent of a history of liver disease, your doctor will consider regular blood tests to check how your liver is working.
- **TRIEMTA TABLETS** may cause inflammation of the pancreas. Inform your doctor if you experience severe upper stomach pain with nausea (feeling sick) and vomiting.
- Inform your doctor if you have had any liver disease including hepatitis B or C, as treatment with **TRIEMTA TABLETS** in patients with liver disease could cause severe side effects affecting the liver including death. Your doctor will monitor your liver function by performing blood tests on a regular basis.
- If you have an ongoing hepatitis B infection, do not stop **TRIEMTA TABLETS** without your doctor's advice, as your hepatitis may come back. The hepatitis may be more severe if you also have a serious liver disease.
- Tell your doctor if you are taking other medicines that contain efavirenz, emtricitabine, tenofovir disoproxil, or lamivudine or adefovir dipivoxil. **TRIEMTA TABLETS** should not be taken with any of these medicines.
- Tell your doctor if you have had kidney disease, or if tests have shown problems with your kidneys. **TRIEMTA TABLETS** may affect your kidneys.
- Rashes may be caused by **TRIEMTA TABLETS**. If you see any signs of a severe rash with blistering or fever, stop taking **TRIEMTA TABLETS** and tell your doctor at once.
- Tell your doctor if you have a history of mental illness, including depression, or of substance or alcohol abuse. Tell your doctor immediately if you feel depressed, have suicidal thoughts or have strange thoughts.
- Tell your doctor if you ever had seizures or are taking medicines for seizures.
- Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms inform your doctor.
- **TRIEMTA TABLETS** decreases bone mineral density which could result in fractures. Your doctor may prescribe calcium and vitamin D supplements while taking **TRIEMTA TABLETS.**
- **TRIEMTA 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 **TRIEMTA TABLETS** is started. If you notice signs of inflammation or infection, or deterioration thereof, tell your doctor at once.
- You will need to take **TRIEMTA TABLETS** every day. **TRIEMTA 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 **TRIEMTA 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.
- **TRIEMTA TABLETS** is not recommended for the elderly who are more than 65 years of age.
- **TRIEMTA 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 TRIEMTA TABLETS with food and drink:
TRIEMTA TABLETS should be taken on an empty stomach. Alcohol should be avoided as well as grapefruit juice.

Pregnancy and breastfeeding:
- Do not take **TRIEMTA TABLETS** if you are pregnant. Malformations have been seen in foetuses from animals treated with **TRIEMTA TABLETS** during pregnancy; therefore, pregnancy should be avoided in women receiving **TRIEMTA TABLETS.**
- Inform your doctor immediately if you are pregnant or intend to become pregnant.
- If you are a woman receiving **TRIEMTA 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). Use adequate contraceptive measures for 12 weeks after discontinuation of **TRIEMTA TABLETS.**
- Do not breastfeed if you are taking **TRIEMTA TABLETS**

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

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

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

- Tell your doctor if you are taking, or have recently taken any other medicines.
- Tell your doctor if you are taking efavirenz, abacavir, emtricitabine, tenofovir, indinavir or lamivudine (for HIV infection).
- If you are currently taking any of the following medicines:
  - 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).
  - terfenadine (used to treat hay fever or other allergies)

If you are taking any of these medicines, tell your doctor immediately as you should not take any of these medicines together with TRIEMTA TABLETS.
- 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 **TRIEMTA TABLETS**.
- Tell your doctor if you are taking other medicines containing didanosine (for HIV infection). Taking **TRIEMTA 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. **TRIEMTA 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, phenobarbitone. **TRIEMTA TABLETS** can reduce the amount of the anticonvulsant in your blood. Carbamazepine can reduce the amount of efavirenz, one of the components of **TRIEMTA 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): Posaconazole, itraconazole or ketoconazole. **TRIEMTA TABLETS** can reduce the amount of posaconazole, 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 **TRIEMTA 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 **TRIEMTA 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) should not be taken with **TRIEMTA TABLETS.**
- Atovaquone/proguanil or artemether/lumefantrine (Medicines used to treat malaria). **TRIEMTA TABLETS** may reduce the amount of atovaquone/proguanil or artemether/ lumefantrine in your blood.
- 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)
  - Aciclovir(for viral infection)
  - Valaciclovir (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 TRIEMTA TABLETS
Do not share your medicines with others.

Always take **TRIEMTA 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 **TRIEMTA TABLETS** is too strong or too weak, talk to your doctor or pharmacist.

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

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

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

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

If any of the following happens, stop taking **TRIEMTA TABLETS** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Hives;
- difficulty breathing;
- swelling of your face, lips, tongue, or throat.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **TRIEMTA TABLETS**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
- 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).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:
Frequent side effects:
- weight gain
- dizziness
- drowsiness
- difficulty falling asleep
- unusual dreams
- headache
- disturbances of co-ordination and balance
- feeling depressed or anxious
- nausea, vomiting
- diarrhoea or constipation
- stomach pain
- indigestion
- upset stomach
- increased appetite
- lack of appetite
- flatulence
- skin rash
- itching
- changes in skin and nail colour
- fatigue or lack of energy
- generally feeling unwell
- pain

Less frequent side effects:
- weight loss
- numbness, tingling, pins and needles
- tremor (shake)
- confusion, forgetfulness, difficulty concentrating, abnormal thinking, feeling agitated, inappropriate behaviour, lack of interest, abnormally happy mood, frequent mood changes, problems with speech, loss of control of bodily movements, loss of sensitivity to touch
- abnormal vision, blurred vision
- ringing in the ears, a feeling of spinning or tilting (vertigo)
- palpitations (rapid irregular action of heart), increased rate of heart beat
- asthma, shortness of breath, cough, runny or stuffy nose, sinusitis, chest infections
- taste disturbances, heartburn
- inflammation of the pancreas (severe pain in the abdomen)
- hives, eczema, loss of hair, acne, skin exfoliation, infection of the hair follicles, allergic skin reaction to sunlight
- joint pain, breakdown of muscle, muscle pain or weakness, back pain, chest pain, softening of the bones (with bone pain and sometimes resulting in fractures)
- impotence (loss of male sexual ability); increased and decreased sexual drive (libido), enlarged breasts in males
- fainting, alcohol intolerance, hot flushes, flu-like symptoms
- 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)
- increased sweating, fever

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

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

STORING AND DISPOSING OF TRIEMTA TABLETS
Store at or below 25 °C (room temperature). Protect from light and moisture. Keep the HDPE containers closed.
KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

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

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

IDENTIFICATION OF TRIEMTA 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
51/20.2.8/0121.120

NAME AND ADDRESS OF REGISTRATION HOLDER
Macleods Pharmaceuticals SA (Pty) Ltd.
Office Block 1,
Bassonia Estate Office Park (East),
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DATE OF PUBLICATION
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SKEDULERINGSTATUS:
S4

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

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

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

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

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

Weerstand:
Efavirens, emtrisitabien en tenofovir disoproksielfumaraat:
MIV-isolate met verminderde vatbaarheid vir die emtrisitabien en tenofovir-kombinasie is *in vitro* geselekteer.
Na genotipiese ontleding is die M184V/I en/of K65R aminosuurvervangings in die virus TT geïdentifiseer.
Efavirens:
Kliniese isolate met verminderde vatbaarheid *in vitro* teen efavirens is verkry. Die mees dikwels waargenome aminosuurvervanging wat in kliniese studies met efavirens waargeneem is, is K103N (54 %). Een of meer TT-vervangings by aminosuurposisies 98, 100, 101, 103, 106, 108, 188, 190, 225, 227 en 230 is waargeneem in pasiënte in wie die behandeling met efavirens in kombinasie met ander antiretrovirusmiddels misluk het. Ander weerstandige mutasies wat dikwels ontwikkel sluit L100I (7 %), K101E/Q/R (14 %), V108I (11 %), G190S/T/A (7 %), P225H (18 %) en M230I/L (11 %) in.
MIV-isolate met verminderde vatbaarheid vir efavirens (meer as 380-voudige toename in EK_{90} waarde) het vinnig onder seleksie *in vitro* ontwikkel. Genotipiese karakterisering van hierdie virusse het mutasies geïdentifiseer wat tot enkel aminosuurvervangings L100I of V179D, dubbel vervangings L100I/V108I en driedubbel vervangings L100I/V179D/Y181C in TT gelei het.
Emtrisitabien:
MIV-isolate wat weerstand teen emtrisitabien bied is *in vitro* geselekteer. Genotipiese onteding van hierdie isolate het aangetoon dat 'n afname in die vatbaarheid teen emtrisitabien met 'n mutasie in die MIV TT-geen by kodon 184 geassosieer is. Hierdie mutasie het 'n aminosuurvervanging van metionien deur valien of isoleusien (M184V/I) veroorsaak.
Tenofovir disoproksielfumaraat:
Isolate van MIV-1 wat verminderde vatbaarheid vir tenofovir getoon het is *in vitro* geselekteer. Hierdie virusse het 'n K65R mutasie in trutranskriptase aangetoon en 'n 2- tot 4-voudige afname in vatbaarheid teen tenofovir getoon.

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

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

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

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

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

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

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

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

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

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

Pasiënte met ingekorte lewerfunksie:
Efavirens:
Die farmakokinetika van efavirens is nie voldoende in pasiënte met ingekorte lewerfunksie bestudeer nie (sien **WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS**).

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

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

KONTRA-INDIKASIES:
TRIEMTA TABLETS word teenaangedui in pasiënte:
- Met voorheen aangetoonde hipersensitiwiteit teen efavirens, emtrisitabien of tenofovir of enige ander van die komponente van **TRIEMTA TABLETS**.
- Met erg ingekorte lewerfunksie (Child-Pugh klas C).
- 'n Geskiedenis van vorige lewerbesering/mislukking met antiretrovirale behandeling (ART) wat efavirens bevat.
- Met matig tot erg ingekorte nierfunksie (kreatinienopruiming < 50 mℓ/min (sien **WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS** en **DOSIS EN GEBRUIKSAANWYSINGS**).
- Wat huidiglik behandeling met kisapried, midasolam, triasolam of ergotderivate ontvang, aangesien kompetisie vir CYP 3A4 deur die efavirens in **TRIEMTA TABLETS** tot inhibisie van die metabolisme van hierdie medisyne kan lei, asook die potensiaal vir ernstige en/of lewensbedreigende newe-effekte (bv. hartdisritmieë, verlengde sedering of respiratoriese onderdrukking) kan ontwikkel.
- Pasiënte wat huidiglik vorikonasool gebruik, aangesien efavirens die plasmakonsentrasie van vorikonasool beduidend laat afneem, terwyl vorikonasool die plasmakonsentrasie van efavirens aansienlik laat toeneem. Aangesien **TRIEMTA TABLETS** 'n vaste dosis kombinasieproduk is, kan die dosis van efavirens nie verander word nie. Daarom behoort vorikonasool en **TRIEMTA TABLETS** nie saam toegedien te word nie.
- Wat swanger is of borsvoed (sien **SWANGERSKAP EN LAKTASIE**).
- Wie gebruik gelyktydig St. John's se kruid (*Hypericum perforatum*) of St John's se kruid-bevattende medisyne (sien **INTERAKSIES**).
- **TRIEMTA TABLETS** word nie aanbeveel vir gebruik in kinders en adolessente jonger as 18 jaar oud weens 'n gebrek aan data oor veiligheid en effektiwiteit.

WAARSKUWINGS EN SPESIALE VOORSORGSMAATREËLS:

MELKSUURASIDOSE EN ERGE HEPATOMEGALIE MET STEATOSE, INSLUITENDE FATALE GEVALLE IS MET DIE GEBRUIK VAN NUKLEOSIEDANALOË, ALLEEN OF IN KOMBINASIE MET ANDER ANTIRETROVIRUSMIDDELS AANGEMELD.
TRIEMTA TABLETS WORD NIE VIR DIE BEHANDELING VAN CHRONIESE HEPATITIS B VIRUS (HBV) INFEKSIE NIE AANGEDUI EN DIE VEILIGHEID EN EFFEKTIWITEIT VAN TRIEMTA TABLETS IS NIE IN PASIËNTE WAT MET BEIDE HBV EN MIV-1 BESMET IS, VASGESTEL NIE. ERGE AKUTE AGTERUITGANG VAN HEPATITIS B IS IN PASIËNTE AANGEMELD WAT MET DIE GEBRUIK VAN EMTRISITABIEN OF TENOFOVIR DF OPGEHOU HET.
IN SOMMIGE VAN DIE PASIENTE WAT MET EMTRISITABIEN BEHANDEL IS, AGTERUITGANG VAN HEPATITIS B, WAS VERBAND MET LEWERDEKOMPENSASIE EN LEWERVERLIES. LEWERFUNKSIE BEHOORT NOUKEURIG MET BEIDE KLINIESE EN LABORATORIUMOPVOLG VIR TEN MINSTE ETLIKE MAANDE GEMONITOR TE WORD IN PASIËNTE WAT MET DIE GEBRUIK VAN TRIEMTA TABLETS OPGEHOU HET EN MET BEIDE MIV EN HBV BESMET IS. INDIEN VAN TOEPASSING KAN DIE INSTELLING VAN ANTI-HEPATITIS B TERAPIE GEREGVERDIG WORD.

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

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

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

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

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

Daar is 'n paar bewyse dat efavirenz geassosieer word met die kliniese patologiese patrone van geneesmiddelinduceerde lewerversaking in MIV-positiewe pasiënte waarvan die sub-massiewe nekrose histologiese patroon blyk te wees geassosieer met 'n hoë morbiditeits- / mortaliteit risiko en kan aanwesig wees baie maande na terapie geïnisieer of selfs gestop is. Risikofaktore sluit in jonger ouderdom, CD4 + tellings ≥350 selle / µl en vroulike geslag.

Vroeë opsporing en behandeling van die lewerversaking en die onmiddellike staking van **TRIEMTA TABLETS** of efavirenz wat medisyne bevat, moet beklemtoon word. Pasiënte wat behandeling met **TRIEMTA TABLETS** gestaak het, moet opvolg vir simptome / tekens van lewerversaking tot 12 maande.

TRIEMTA TABLETS word nie aanbeveel by pasiënte met matige tot ernstige lewerfardigheid nie, aangesien daar nie genoeg data is om vas te stel of dosisaanpassings benodig word nie.

Lewerensieme:
Die monitering van lewerensiemvlakke 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 **TRIEMTA TABLETS** behoort teen die onbekende risiko van noemenswaardige lewertoksisiteit opgeweeg te word in pasiënte wat aanhoudende verhogings van serumtransaminases na meer as 5 keer die boonste limiet van normaal van die normale reikwydte toon (sien **NEWE-EFFEKTE**).

Pasiënte op **TRIEMTA TABLETS** of efavirenz wat antiretrovirale behandeling (ART) bevat, moet gereeld gemonitor word vir geelsug (insluitend laboratorium bilirubien en lewer ensieme) en bloedingstendense.

Pasiënte met beide MIV en hepatitis B of C infeksie:
Daar word aanbeveel dat alle pasiënte met MIV getoets word vir die teenwoordigheid van chroniese HBV voordat anti-retrovirale terapie begin word. **TRIEMTA TABLETS** is nie aangedui vir die behandeling van chroniese HBV infeksie nie en veiligheid en effektiwiteit van **TRIEMTA TABLETS** is nie vasgestel by pasiënte wat saam met HBV en MIV geïnfekteer is nie. Ernstige akute verergerings van hepatitis B is aangemeld by pasiënte wat met beide MIV en HBV besmet is en wat emtrisitabien of tenofovir DF gestaak het. In sommige van hierdie pasiënte wat behandel is met emtrisitabien, is die verergering van hepatitis B geassosieer met lewerafbreking en lewerversaking. Pasiënte wat met beide MIV en HBV besmet is en wat met die gebruik van **TRIEMTA TABLETS** staak, behoort noukeurig met beide kliniese en laboratoriumopvolg na staking van die terapie opgevolg te word. Indien nodig, kan inisiasie van anti-hepatitis B-terapie geregverdig word.

Pasiënte met chroniese hepatitis B of C en wat met antiretrovirus terapie behandel word, het 'n groter risiko vir erge en potensieel fatale newe-effekte van die lewer.
Mediese praktisyns behoort na die huidige MIV-behandelingsriglyne te verwys vir die optimale bestuur van MIV-infeksie in pasiënte wat ook met hepatitis B virus (HBV) besmet is.
In die geval van meegaande antivirusterapie vir hepatitis B of C, moet ook na die relevante voubiljette vir hierdie medisyne verwys word.

In pasiënte met gevorderde lewersiekte of -sirrose, word die staking van terapie nie aanbeveel nie, aangesien die agteruitgang van hepatitis na behandeling tot lewerdekompensering kan lei.
Die staking van **TRIEMTA TABLETS** in pasiënte wat met beide MIV en HBV besmet is, kan met erge agteruitgang van hepatitis geassosieer word.

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

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

Psigiatriese simptome:
Ernstige psigiatriese newe-effekte is in pasiënte wat met efavirens behandel is, aangemeld. Hierdie newe-effekte sluit in: erge depressie, selfmoordidees, nie-fatale selfmoordpogings, aggressiewe gedrag, paranoïese gedagtes en maniese gedagtes. Behandeling met efavirenz word geassosieer met 'n toename in die voorkoms van hierdie psigiatriese simptome.
Daar bestaan ook nabemarkingsvermeldings van dood deur selfmoord, delusies en psigoseagtige gedrag; 'n oorsaaklike verwantskap met die gebruik van efavirens kan egter nie uit hierdie vermeldings vasgestel word nie. Pasiënte met ernstige psigiatriese newe-effekte behoort onmiddellik mediese evaluering te ondergaan om vas te stel om die moontlikheid dat die simptome kan verband hou met die gebruik van efavirenz, dus **TRIEMTA TABLETS** evalueer.

Afwykings van die senuweestelsel :
Hierdie simptome ingesluit duiseligheid, slaaploosheid, ingekorte konsentrasievermoë, slaapsug, abnormale drome en hallusinasies. Ander aangemelde simptome het euforie, verwarheid, agitasie, amnesie, beneweling, abnormale denke en depersonalisering ingesluit. Hierdie simptome begin gewoonlik gedurende die eerste of tweede dag van terapie en kan na die eerste 2 - 4 weke van terapie oplos. Pasiënte behoort ingelig te word dat hierdie algemene simptome kan verbeter met voortgesette terapie en mag nie voorspelbaar wees van die daaropvolgende aanvang van die minder algemene psigiatriese simptome nie. Dosering met slapenstyd kan die verdraagsaamheid van hierdie simptome van die senuweestelsel verbeter.
Pasiente wat **TRIEMTA TABLETS** ontvang behoort gewaarsku te word teen die potensiaal vir bykomende simptome van die sentrale senuweestelsel wanneer **TRIEMTA TABLETS** saam met alkohol of psigoaktiewe medisyne geneem word.

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

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

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

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

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

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

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

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

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

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

Pediatriese en adolescent gebruik:
Die veiligheid en effektiwiteit van **TRIEMTA TABLETS** is nie in kinders en adolescents jonger as 18 jaar vasgestel nie, daarom **TRIEMTA TABLETS** word nie in hierdie ouderdomsgroep aanbeveel nie.

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

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

INTERAKSIES:
Efavirens:
In vivo is daar aangetoon dat efavirens CYP3A4 en CYP2B6 induseer. Ander middels wat substrate van CYP3A4 is, mag laer plasmakonsentrasies toon wanneer hulle saam met efavirens toegedien word. *In vitro* studies het aangetoon dat efavirens 2C9 en 2C19 isoënsieme in die reikwydte van waargenome plasmakonsentrasies van efavirens inhibeer. Die medetoediening van efavirens saam met medisyne wat hoofsaaklik deur hierdie ensieme gemetaboliseer word, kan tot veranderde plasmakonsentrasies van die medetoegediende medisyne lei.
Daar word verwag dat medisyne wat CYP3A4 aktiwiteit induseer (bv. fenobarbital, rifampien, rifabutien), die opruiming van efavirens sal verhoog, wat tot laer plasmakonsentrasies sal lei. Efavirenz blootstelling kan verhoog word deur medisyne (soos ritonavir) of pomelosap wat CYP3A4 of CYP2B6 aktiwiteit inhibeer.
Emtrisitabien en tenofovir disoproksielfumaraat:
Aangesien emtrisitabien en tenofovir hoofsaaklik deur die niere uitgeskei word, kan die medetoediening van **TRIEMTA TABLETS** saam met middels wat nierfunksie vertraag of vir aktiewe buissekresie kompeteer, die serumkonsentrasies van emtrisitabien, tenofovir en/of ander middels wat deur die niere uitgeskei word, verhoog. Sommige voorbeelde sluit asiklovir, adefovirdipivoksiel, sidofovir, gansiklovir, valasiklovir, valgansiklovir, aminoglikosiede, amfoterisien B, foscarnet, pentamidien en interleukien-2 in, maar is nie tot hierdie middels beperk nie.
Die medetoediening van tenofovir DF en didanosien behoort met sorg onderneem te word en pasiënte wat hierdie kombinasie ontvang, behoort noukeurig vir didanosienverwante newe-effekte gemonitor te word. Didanosien behoort gestaak te word in pasiënte wat didanosienverwante newe-effekte ontwikkel (vir aanbevelings oor doseringsaanpassings vir didanosien, verwys na Tabel 3).
Onderdrukking van die CD4 tellings is in pasiënte wat tenofovir DF saam met didanosien 400 mg daagliks ontvang, waargeneem.
Daar is aangetoon dat atasanavir en lopinavir/ritonavir die konsentrasies van tenofovir verhoog. Die meganisme van hierdie interaksie is nie bekend nie. Hoër tenofovir konsentrasies kan moontlik tenofovirverwante newe-effekte, insluitende nierafwykings, potensieer. Pasiënte wat atasanavir of lopinavir/ritonavir saam met tenofovir ontvang, behoort vir tenofovirverwante newe-effekte gemonitor te word. **TRIEMTA TABLETS** behoort gestaak te word in pasiënte wat tenofovirverwante newe-effekte ontwikkel (vir aanbevelings oor doseringsaanpassings vir didanosien, verwys na Tabel 3).
Ander belangrike inligting oor medisyne interaksies vir **TRIEMTA TABLETS** word in tabel 2 en 3 opgesom. Die interaksies wat beskryf word is gebaseer op studies wat uitgevoer is met efavirens, emtrisitabien of tenofovir DF as individuele middels, of is potensiële interaksies. Geen medisyne interaksiestudies is uitgevoer met die kombinasie van aktiewe soos in **TRIEMTA TABLETS** nie.

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

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

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

Meegaande medisyne Klas: Naam van die medisyne	Effek	Kliniese kommentaar
Antiretrovirusmiddels		
Proteaseïnhibeerder: Amprenavir	↓ Amprenavir-konsentrasie	Efavirens besit die potensiaal om die serumkonsentrasies van amprenavir te verminder
Proteaseïnhibeerder: Fosamprenavirkalsium	↓ Amprenavir-konsentrasie	Fosamprenavir (ongeskraag): Toepaslike dosisse van fosamprenavir en **TRIEMTA TABLETS** ten opsigte van veiligheid en effektiwiteit is nie vasgestel nie. Fosamprenavir/ritonavir: 'n Addisionele 100 mg per dag (300 mg totaal) ritonavir word aanbeveel wanneer **TRIEMTA TABLETS** saam met fosamprenavir een keer per dag toegedien word. Geen verandering in die ritonavir dosis is nodig wanneer **TRIEMTA TABLETS** saam met fosamprenavir/ritonavir toegedien word nie. Geen verandering in die ritonavir dosis is nodig wanneer **TRIEMTA TABLETS** saam met fosamprenavir plus ritonavir twee keer per dag toegedien word nie.
Proteaseïnhibeerder: Atasanavir	↓ atasanavir konsentrasie ↑ tenofovir konsentrasie	Die plasmakonsentrasie van atasanavir is deur beide efavirens en tenofovir DF verminder. Daar is nie voldoende data beskikbaar om 'n dosisaanbeveling vir atasanavir of atasanavir/ritonavir saam met **TRIEMTA TABLETS** te maak nie. Daarom word die medetoediening van **TRIEMTA TABLETS** saam met atasanavir, weens besorgdheid oor die afname van die atasanavir konsentrasie, nie aanbeveel nie.
Proteaseïnhibeerder: Indinavir	↓ indinavir konsentrasie	Die optimale indinavir dosis, wanneer in kombinasie met efavirens toegedien word, is nie bekend nie. Verhoging van die indinavir dosis na 1000 mg elke 8 ure kompenseer nie vir die toename in die metabolisme van indinavir weens efavirens nie.
Proteaseïnhibeerder: Lopinavir/ritonavir	↓ lopinavir konsentrasie ↑ tenofovir konsentrasie	'n Toename in die dosis van lopinavir/ritonavir na 600/150 mg (3 tablette) twee keer per dag kan oorweeg word wanneer dit in kombinasie gebruik word met efavirens in pasiënte wat voorheen behandeling ontvang het en waar 'n afname in die vatbaarheid vir lopinavir klinies vermoed word. **Pasiënte behoort vir tenofovir verwante newe-effekte gemonitor te word. TRIEMTA TABLETS behoort in pasiënte wat tenofovir verwante newe-effekte ontwikkel, gestaak te word.**
Proteaseïnhibeerder: Ritonavir	↑ ritonavir konsentrasie ↑ efavirens konsentrasie	Wanneer ritonavir 500 mg elke 12 ure saam met efavirens 600 mg een keer per dag toegedien word, word die kombinasie geassosieer met 'n hoër frekwensie van nadelige kliniese ondervindings (bv. duiseligheid, naarheid, parestesie), asook laboratoriumabnormaliteite (toename in lewerensieme). Monitering van lewerensieme word aanbeveel wanneer **TRIEMTA TABLETS** in kombinasie met ritonavir gebruik word.
Proteaseïnhibeerder: Sakinavir	↑ sakinavir konsentrasie	Behoort nie as die enigste proteaseïnhibeerder saam met **TRIEMTA TABLETS** gebruik te word nie.
NTTI: Didanosien	↑ didanosien konsentrasie	Hoër didanosien konsentrasies kan didanosienverwante newe-effekte potensieer, insluitende pankreatitis en neuropatie. **In pasiënte wat meer as 60 kg weeg behoort die didanosien dosis na 250 mg verlaag te word as dit saam met TRIEMTA TABLETS toegedien word. Daar is geen data beskikbaar om 'n dosis aanpassing van didanosien vir pasiënte wat minder as 60 kg weeg, aan te beveel nie.** Wanneer saam toegedien word, kan **TRIEMTA TABLETS** en didanosien onder vastende kondisies of met 'n ligte maaltyd (minder as 400 kkal, 20 % vet) geneem word. Die medetoediening van didanosien gebufferde formulasie saam met **TRIEMTA TABLETS** behoort onder vastende kondisies plaas te vind. **Die medetoediening van TRIEMTA TABLETS saam met didanosien behoort met sorg te geskied en pasiënte wat hierdie kombinasie ontvang, behoort noukeurig vir didanosienverwante newe-effekte gemonitor te word.**
Ander middels		
Teenstolmiddel: Warfarien	↑ of ↓ warfarien konsentrasie	Plasmakonsentrasies en effekte word potensieel verhoog of verlaag deur efavirens.
Antistuipmiddel: Karbamasepien	↓ karbamasepien konsentrasie ↓ efavirens konsentrasie	Daar bestaan nie genoeg data om 'n dosis aanbeveling vir **TRIEMTA TABLETS** te maak nie. Alternatiewe antistuipbehandeling behoort gebruik te word.
Fenitoïen Fenobarbital	↓ antistuipmiddel konsentrasie ↓ efavirens konsentrasie	Potensiaal vir afname in antistuip en/of efavirens plasmavlakke; periodieke monitering van antistuip plasmavlakke behoort uitgevoer te word.
Valproïensuur /Efavirens	Geen klinies-belangrike effek op efavirens farmakokinetika. Beperkte data dui daarop dat daar geen klinies-beduidende effek op valproïensuur farmakokinetika is nie.	**TRIEMTA TABLETS** en valproïensuur kan saam toegedien word sonder dosisaanpassing. Pasiënte moet gemoniteer word vir stuiptrekking beheer.
Vigabatrien/Efavirens Gabapentien/Efavirens	Interaksie nie bestudeer nie. Kliniese beduidende interaksies word nie verwag nie aangesien vigabatrien en gabapentien word eksklusief in die urine onveranderd geelimineer en onwaarskynlik is om vir dieselfde metaboliese ensieme en eliminasieweë te kompeteer soos efavirens	**TRIEMTA TABLETS** en vigabatrien of gabapentien kan saam toegedien word sonder dosisaanpassing.
Antidepressant: Sertralien	↓ sertralien konsentrasie	Toenames van die sertraliendosis behoort op grond van die kliniese respons gedoen te word.
Paroksetien/Efavirens	Paroksetien: AOK: ↔ K_{maks}: ↔ K_{min}: ↔ Efavirenz: ↔ AOK: ↔ K_{maks}: ↔ K_{min}: ↔	**TRIEMTA TABLETS** en paroksetien kan saam toegedien word sonder dosisaanpassing.
Fluoksetien/Efavirens	Interaksie nie bestudeer nie. Aangesien fluoksetien 'n soortgelyke metaboliese profiel met paroksetien deel, dws 'n sterk CYP2D6 inhibitoriese effek, sal 'n soortgelyke tekort aan interaksie vir fluoksetien verwag word.	**TRIEMTA TABLETS** en fluoksetien kan saam toegedien word sonder dosisaanpassing.
Swamweerder: Itrakonasool Posakonasool Ketokonasool	↓ itrakonasool konsentrasie ↓ hidroksie-itrakonasool konsentrasie ↓ posakonasool ↓ ketokonasool konsentrasie	Aangesien geen dosisaanpassing vir itrakonasool gemaak kan word nie, behoort alternatiewe swamwerende behandeling oorweeg te word. Gelyktydige gebruik moet vermy word. Middel interaksiestudies met **TRIEMTA TABLETS** en ketokonasool is nie uitgevoer nie. Efavirens besit die potensiaal om die plasmakonsentrasies van ketokonasool te verlaag.
Anti-infektiewe middels: Klaritromisien	↓ klaritromisien konsentrasie ↑ 14-OH metaboliet konsentrasie	Die kliniese betekenis hiervan is onbekend. In onbesmette vrywilligers het 46 % egter uitslag ontwikkel terwyl hulle efavirens en klaritromisien ontvang het. Geen dosisaanpassing van **TRIEMTA TABLETS** word aanbeveel wanneer dit saam met klaritromisien toegedien word nie. Alternatiewe vir klaritromisien, soos asitromisien behoort oorweeg te word. Ander makroliede antibiotika soos eritromisien is nie in kombinasie met **TRIEMTA TABLETS** bestudeer nie.
Antimikobakteriële middels: Rifabutien	↓ rifabutien konsentrasie	Verhoog die daaglikse rifabutien dosis met 50 %. Oorweeg die verdubbeling van die rifabutien dosis in regimens war rifabutien twee of drie keer per week toegedien word.
Antimikobakteriële middels: Rifampisien	↓ efavirens konsentrasie	Die kliniese betekenis van 'n laer efavirens konsentrasie is nie bekend nie. Geen doseringsaanbevelings vir die gelyktydige gebruik van **TRIEMTA TABLETS** en rifampisien is vasgestel nie.
Kalsiumkanaalblokkeerders: Diltiasem	↓ diltiasem konsentrasie ↓ desasetiel-diltiasem konsentrasie	Dosering van diltiasem behoort op grond van die kliniese respons uitgevoer te word. Geen dosisaanpassing vir **TRIEMTA TABLETS** is nodig wanneer dit saam met diltiasem toegedien word nie.
Ander (bv. felodipien, nifedipien, nikardepien, verapamiel)	↓ N-monodesmetieldiltiasem konsentrasie ↓ kalsiumkanaal-blokkeerder	Daar bestaan geen data oor die potensiële interaksies met ander kalsiumkanaal-blokkeerders wat substrate vir CYP3A4 ensieme is nie. Daar bestaan 'n potensiaal vir die afname in plasmakonsentrasie van die kalsiumkanaalblokkeerder. Die dosis behoort op grond van die kliniese respons aangepas te word.
HMG-KoA reduktase-inhibeerders: Atorvastatien, pravastatien, simvastatien	↓ atorvastatien konsentrasie ↓ pravastatien konsentrasie ↓ simvastatien konsentrasie	Die plasmakonsentrasies van atorvastatien, pravastatien en simvastatien het met efavirens afgeneem. Raadpleeg die volledige vou-biljette van die HMG-KoA reduktaseïnhibeerder vir riglyne oor individualisering van die dosis.
Narkotiese pynstiller: Metadoon	↓ metadoon konsentrasie	Die medetoediening van efavirens in MIV-1 besmette individue met 'n geskiedenis van inspuitbare medisyne gebruik het tot 'n afname in die plasmavlakke van metadoon en tekens van opiaatonttrekking gelei. Die metadoon dosis is met gemiddeld 22 % verhoog om die onttrekkingsimptome te verlig. Pasiënte behoort vir tekens van onttrekking gemonitor te word en hul metadoon dosis soos nodig verhoog te word om die simptome van onttrekking te verlig.
Orale voorbehoedmiddels: Etinielestradiol	↑ etinielestradiol konsentrasie	Die kliniese betekenis hiervan is nie bekend nie. Omdat die potensiële interaksie met orale voorbehoedmiddels nog nie ten volle gekenmerk is nie, behoort 'n betroubare vorm van skeidingskontrasepsie bykomend tot die orale voorbehoedmiddel gebruik te word.
Artemether / Lumefantrien / Efavirens (20/120 mg tablet, 6 dosisse van 4 tablette elk oor 3 dae / 600 mg per dag.)	Artemether: AOK: ↓ 51 % K_{maks}: ↓ 21 % Dihydroartemisinien (aktiewe metaboliet): AOK: ↓ 46 % K_{maks}: ↓ 38 % Lumefantrien: AOK: ↓ 21 % K_{maks}: ↔ Efavirens: AOK: ↓ 17 % K_{maks}: ↔ (CYP3A4 induksie)	Aangesien afgeneem konsentrasies van artemether, dihydroartemisinien of lumefantrien kan lei tot 'n afname in antimalariëre effektiwiteit, word versigtigheid aanbeveel wanneer **TRIEMTA TABLETS** en artemether/lumefantrine tablette saam toegedien word.
Atovaquone en Proguanil Hidrochloried / Efavirens (250/100 mg enkel dosis / 600 mg daagliks.)	Atovaquone: AOK: ↓ 75 % (↓ 62 to ↓ 84) K_{maks}: ↓ 44 % (↓ 20 to ↓ 61) Proguanil: AOK: ↓ 43 % (↓ 7 to ↓ 65) K_{maks}: ↔	Gelyktydige toediening van atovaquone/proguanil met **TRIEMTA TABLETS** moet vermy word waar moontlik.

[1] Hierdie tabel is nie allesinsluitend nie

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

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

SWANGERSKAP EN LAKTASIE:
Swangerskap:
Die gebruik van **TRIEMTA TABLETS** gedurende swangerskap word teenaangedui.
Efavirens:
Daar is berigte van bevindings wat ooreenstem met neurale buisdefekte, insluitende meningomyelocele, almal in moeders wat in die eerste trimester aan efavirenz-bevattende regimente blootgestel is. Aangesien neurale buisdefekte binne die eerste 4 weke van fetale ontwikkeling voorkom (wanneer neurale buise verseël word), sal hierdie potensiële risiko betrekking hê op vroue wat gedurende die eerste trimester van swangerskap blootgestel is aan efavirens.
Misvormings is waargeneem in fetusse van efavirens-behandelde ape.
Skeidingskontrasepsie behoort altyd in kombinasie met ander metodes van kontrasepsie (bv. orale of hormonale kontrasepsie) gebruik te word). As gevolg van die lang halveleeftyd van efavirens, word aanbeveel om voldoende kontrasepsiemaatreëls vir 12 weke na die staking van **TRIEMTA TABLETS** te gebruik.
Vroue wat kan swanger raak behoort swangerskapstoetsing te ondergaan vóór inisiëring van behandeling met **TRIEMTA TABLETS**.

Moeders wat borsvoed: MIV-positiewe moeders behoort nie hul babas te borsvoed nie. Efavirenz, emtrisitabien en tenofovir word in menslike melk uitgeskei. Weens die potensiaal vir MIV-oordraging en die potensiaal vir ernstige newe-effekte in sogende babas, **behoort moeders aangesê te word om nie hul babas te borsvoed as hulle TRIEMTA TABLETS neem nie**.

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

NEWE-EFFEKTE:
EFAVIRENS
Afwykings van die immuunstelsel:
Minder dikwels: Hipersensitiwiteit.
Frekwensie onbekend: Immuno-allergiese lewer besering/ lewerversaking.
Metaboliese en voedingsafwykings:
Dikwels: Massatoename, hipertrigliseridemie.
Minder dikwels: Hipercholesterolemie.
Frekwensie onbekend: Massaverlies, herverspreiding/akkumulasie van liggaamsvet.
Psigiatriese afwykings:
Dikwels: Depressie, angs, abnormale drome, slaaploosheid.
Minder dikwels: Beneweling, verwardheid, ingekorte konsentrasievermoë, abnormale denke, geroer, amnesie, delirium, emosionele onstabiliteit, euforie, hallusinering, psigose, selfmoordidees en –pogings, voltooide selfmoord, vervolgingswaan, manie, delusies, neurose.
Frekwensie onbekend: Ontoepaslike gedrag, apatie.
Afwykings van die senuweestelsel:
Dikwels: Duiseligheid, hoofpyn, slaapsug, cerebellaire koordinasie en balansversteuring, versteuring van aandag.
Minder dikwels: Abnormale koördinasie, ataksie, stuipaanvalle, migraine hoofpyne, neuralgie, parestesie, perifere neuropatie, spraakafwyking, bewerasie, hipoëstesie, amnesie, abnormale denke, geroer.
Oogafwykings:
Minder dikwels: Abnormale visie, versteurde visie.
Afwykings van die oor en labirint:
Minder dikwels: Tinnitus, vertigo.
Hartafwykings:
Minder dikwels: Hittegloede, hartkloppings tagikardie.
Respiratoriese, bors- en mediastinale afwykings:
Minder dikwels: Asma, boonste lugweginfeksies, sinusitis.
Frekwensie onbekend: Dispnee.
Gastroïntestinale afwykings:
Dikwels: Naarheid, braking, diarree, bruikpyn.
Dikwels: Gastritis, gastroënteritis, gastro-esofagale refluks, toename in eetlus, smaakafwykings, pankreatitis.
Frekwensie onbekend: Hardlywigheid, wanabsorpsie.
Hepatobileêre afwykings:
Dikwels: Verhoogde aspartate aminotransferase (AST), verhoogde alanine aminotransferase (ALT), verhoogde gamma-glytamyltransferase (GGT).
Minder dikwels: Hepatitis, lewerversaking.
Afwykings van die vel en subkutane weefsels:
Dikwels: Verspreide makulopapulêre uitslag, pruritus.
Minder dikwels: Erge uitslag geassosieer met blaasvorming, vogtige velafskilfering of -ulserasie, aknee, alopesie, ekseem, follikulitis, seborree, velafskilfering, urtikarie, erythema multiforme, foto-allergiese dermatitis, Stevens-Johnson se sindroom.
Frekwensie onbekend: Naelafwykings, velverkleuring.
Muskuloskeletale, bindweefsel- en beenafwykings:
Minder dikwels: Artralgie, mialgie.
Frekwensie onbekend: Miopatie.
Reproduksiestelsel- en borsafwykings:
Minder dikwels: Impotensie, afname in libido, toename in libido, ginekomastie.
Algemene afwykings en kondisies by die plek van toediening:
Dikwels: Moegheid.
Minder dikwels: Astenie, malaise, pyn, sinkopee, griepagtige simptome, alkoholintoleransie, hittegloede.

EMTRISITABIEN:
Afwykings van die bloed- en limfsisteem:
Dikwels: Neutropenie.
Minder dikwels: Anemie.
Immuniteitstelsel versteurings:
Dikwels: Allergiese reaksie.
Metaboliese en voedingsafwykings:
Dikwels: Hipertrigliseridemie, hiperglukemie.
Frekwensie onbekend: Melksuurasidose, gewoonlik geassosieer met erge hepatomegalie en steatose.
Psigiatriese afwykings:
Dikwels: Slaapafwykings (abnormale drome, slaaploosheid).
Frekwensie onbekend: Depressie afwyking.
Afwykings van die senuweestelsel:
Dikwels: Hoofpyn, duiseligheid.
Frekwensie onbekend: Astenie, neuropatie, perifere neuritis, parestesie.
Gastroïntestinale afwykings:
Dikwels: Naarheid, braking, diarree, verhoogde amilase insluitend verhoogde pankreasamilase, verhoogde serumℓipase, buikpyn, dispepsie.
Hepatobileêre afwykings:
Dikwels: Toename in lewerensiemkonsentrasies en hiperbilirubinemie.
Afwykings van die vel en subkutane weefsels:
Dikwels: Uitslagepisodes (insluitende uitslag, pruritus, makulopapulêre uitslag, urtikarie, vesikobulleuse uitslag, pustulêre uitslag en allergiese reaksie), velverkleuring, gemanifesteer deur hiperpigmentasie op die handpalms en/of voetsole.
Minder dikwels: Angioedema.
Muskuloskeletale, bindweefsel- en beenafwykings:
Minder dikwels: Verhoogde kreatinien kinase.
Frekwensie onbekend: Artralgie, mialgie.
Respiratoriese, bors- en mediastinale afwykings:
Frekwensie onbekend: Toename in hoes en rinitis.
Algemene afwykings en kondisies by die plek van toediening:
Dikwels: Pyn, astenie.

TENOFOVIR:
Afwykings van die bloed- en limfsisteem:
Frekwensie onbekend: Neutropenie, hematurie.
Afwykings van die immuunstelsel:
Frekwensie onbekend: Allergie, allergiese reaksies.
Metaboliese en voedingsafwykings:
Dikwels: Hipofosfatemie.
Minder dikwels: Hipokalemie, melksuurasidose, gewoonlik geassosieer met erge hepatomegalie en steatose.
Frekwensie onbekend: hipertrigliseridemie, hiperglukemie.
Psigiatriese afwykings:
Frekwensie onbekend: Depressie, angs.
Afwykings van die senuweestelsel:
Baie dikwels: Duiseligheid, hoofpyn.
Frekwensie onbekend: Perifere neuropatie (insluitende perifere neuritis, neuropatie).
Respiratoriese, bors- en mediastinale afwykings:
Frekwensie onbekend: Borspyn, pneumonie, dispnee.
Gastroïntestinale afwykings:
Dikwels: Naarheid, braking, diarree, buikpyn, winderigheid, dispepsie en anoreksie.
Minder dikwels: Verhoogde serumamilase konsentrasie, pankreatitis.
Hepatobileêre afwykings:
Dikwels: Verhoogde lewerensieme.
Minder dikwels: Hepatiese steatose, hepatitis.
Afwykings van die vel en subkutane weefsels:
Dikwels: Veluitslag (insluitende uitslag, pruritus, makulopapulêre uitslag, urtikarie, vesikobulleuse uitslag, pustulêre uitslag).
Minder dikwels: Angioedema.
Muskuloskeletale en bindweefselafwykings:
Minder dikwels: Rabdomiolise, spierswakheid, osteomalasie (gemanifesteer as been pyn en selde by te dra tot frakture), miopatie.
Frekwensie onbekend: Rugpyn, artralgie, mialgie.
Nier- en urienafwykings:
Minder dikwels: Proteïenurie, proksimale tubulopatie insluitende Fanconi se sindroom, nierversaking (akute en chroniese), akute buisnekrose, nefritis (insluitende akute interstisiële nefritis), nefrogeniese diabetes insipidus.
Frekwensie onbekend: Nier waardedaling.
Algemene afwykings en kondisies by die plek van toediening:
Dikwels: Astenie.
Frekwensie onbekend: Koors, sweet, massaverlies.

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

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

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

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

REGISTRASIENOMMER:
51/20.2.8/0121.120

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

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INLIGTINGSBLAD VIR PASIËNTE

SKEDULERINGSTATUS:
S4

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

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

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

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

VOORDAT U TRIEMTA TABLETS NEEM
Moenie TRIEMTA TABLETS neem nie:
- As u hipersensitief (allergies) teen efavirens, emtrisitabien en tenofovir disoproksielfumaraat of enige van die ander bestanddele van **TRIEMTA TABLETS** is
- As u aan nierprobleme ly.
- As u aan lewerprobleme ly.
- As u 'n lewerversteuring of lewerversaking gehad het wat toegeskryf word aan behandeling met **TRIEMTA TABLETS.**
- As u swanger is of borsvoed.
- As u tans enige van die volgende medisyne gebruik:
  - kisapried (gebruik om sooibrand te behandel)
  - bepridiel (gebruik om hartsiekte te behandel)
  - ergotalkaloïede (bv. ergotamien, dihidroërgotamien, ergonovien en metielergonovien) (gebruik om migraine en troshoofpyne te behandel)
  - midasolam of triasolam (gebruik om u te help slaap)
  - pimosied (gebruik om sekere geestessiektes te behandel)
  - vorikonasool (vir swaminfeksies).
  - terfenadine (gebruik om hooi koors of ander allergieë behandel)
  - St. John's se kruid *(Hypericum perforatum)* ('n kruiemiddel gebruik vir depressie en angs).

As u enige van die hierdie medisyne gebruik, moet u onmiddellik u dokter in kennis stel. Die neem van hierdie medisyne saam met **TRIEMTA TABLETS** kan ernstige of lewensbedreigende newe-effekte veroorsaak of kan veroorsaak dat hierdie medisyne nie werk nie.
- Die veiligheid en doeltreffendheid van **TRIEMTA TABLETS** in kinders en pasiënte jonger as 18 jaar is nie vasgestel nie. Daarom moet dit nie by pasiënte jonger as 18 jaar gebruik word nie.

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

Die neem van TRIEMTA TABLETS saam met voedsel en vloeistof:
TRIEMTA TABLETS behoort sonder voedsel geneem te word. Alkohol behoort vermy te word, asook pomelosap.

Swangerskap en borsvoeding:
- Moenie **TRIEMTA TABLETS** vat as u swanger is. Misvormings is in fetusse van diere wat met **TRIEMTA TABLETS** gedurende dragtigheid behandel is, waargeneem, dus, u behoort nie swanger te raak as u **TRIEMTA TABLETS** neem nie.
- Stel u dokter onmiddellik in kennis as u swanger is of beoog om swanger te raak.
- As u 'n vrou is wat **TRIEMTA TABLETS** neem, behoort 'n betroubare vorm van skeidingskontrasepsie (bv. kondoom) altyd gebruik te word saam met ander metodes van voorbehoeding, insluitende orale (die pil) of ander hormonale voorbehoedmiddels (bv. implante, inspuitings) gebruik te word. Gebruik voldoende kontraseptiewe maatreëls vir 12 weke na staking van **TRIEMTA TABLETS**.
- Moenie borsvoed as u **TRIEMTA TABLETS** neem nie aangesien dit ernstige skade aan u baba kan verrig.

As u swanger is of u baba borsvoed, moet u asseblief u dokter, apteker of ander gesondheidsbeampte vir advies nader voordat u **TRIEMTA TABLETS** neem.

Bestuur en die gebruik van masjinerie:
TRIEMTA TABLETS kan duiseligheid, ingekorte konsentrasievermoë en/of lomerigheid veroorsaak. As u duiselig of lomerig voel terwyl u **TRIEMTA TABLETS** neem moet u nie bestuur of met enige gereedskap of masjinerie werk nie.
Stel altyd u professionele gesondheidswerker in kennis as u enige ander medisyne neem. (Dit sluit komplementêre en tradisionele medisyne in.)

Die neem van ander medisyne saam met TRIEMTA TABLETS:
Stel altyd u professionele gesondheidswerker in kennis as u enige ander medisyne neem. (Dit sluit komplementêre en tradisionele medisyne in.)

- Stel u dokter in kennis as u enige ander medisyne gebruik of onlangs gebruik het.
- Stel u dokter in kennis as u efavirens, abasavir, emtrisitabien, tenofovir, indinavir of lamivudien (vir MIV-infeksie) neem.
- As u tans enige van die volgende medisyne neem:
  - astemizole (gebruik om hooikoors of ander allergieë te behandel)
  - kisapried (gebruik om sooibrand te behandel)
  - bepridiel (gebruik om hartsiekte te behandel)
  - ergotalkaloïede (bv. ergotamien, dihidroërgotamien, ergonovien en metielergonovien) (gebruik om migraine en troshoofpyne te behandel)
  - midasolam of triasolam (gebruik om u te help slaap)
  - pimosied (gebruik om sekere geestessiektes te behandel)
  - vorikonasool (vir swaminfeksies).
  - terfenadine (gebruik om hooikoors of ander allergieë te behandel).

As u enige van hierdie medisyne neem, moet u onmiddellik u dokter daarvan in kennis stel aangesien u nie saam met TRIEMTA TABLETS enige van hierdie medisyne moet gebruik nie

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

HOE OM TRIEMTA TABLETS TE NEEM
Moenie jou medisyne met ander deel nie.

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

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

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

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

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

MOONTLIKE NEWE-EFFEKTE
TRIEMTA TABLETS kan newe-effekte hê.
Nie al die newe-effekte wat vir hierdie medisyne aangemeld is, word in hierdie brosjure ingesluit nie. As u algemene gesondheid agteruitgaan of as u enige ongewone effekte ondervind terwyl u **TRIEMTA TABLETS** neem, moet u asseblief u dokter, apteker of ander professionele gesondheidswerker om advies raadpleeg.
Indien enige van die volgende gebeur, stop met die neem van **TRIEMTA TABLETS** en raadpleeg u dokter onmiddellik of gaan na die ongevalle-afdeling by u naaste hospitaal:
- Urtikarie,
- moeite met asemhaling,
- swelling van u gesig, lippe, tong of keel.

Dit is almal baie ernstige newe-effekte. As jy dit het, het jy dalk 'n ernstige allergiese reaksie gehad met **TRIEMTA TABLETS**. Jy mag dringende mediese aandag of hospitalisasie benodig.

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

Dit is almal ernstige newe-effekte. Jy benodig dringende mediese aandag.

Raadpleeg jou dokter as jy enige van die volgende opmerk:
Dikwels voorkomende newe-effekte:
- massatoename
- duiseligheid
- lomerigheid
- moeite om aan die slaap te raak
- abnormale drome
- hoofpyn
- afwykings van koördinasie en balans
- gevoel van depressie of angs
- naarheid, braking
- diarree of hardlywigheid
- maagpyn
- indigestie
- omgekrapte maag
- verhoogde eetlus
- gebrek aan eetlus
- winderigheid
- veluitslag
- jeuk
- veranderinge in vel en spyker kleur
- moegheid or tekort aan energie
- oor die algemeen ongesteld voel
- pyn

Minder dikwels voorkomende newe-effekte:
- gewigsverlies
- gevoelloosheid, prikkeling, spelde en naalde
- bewerasie
- verwardheid, vergeetagtigheid moeite met konsentrasie, vergeetagtigheid, abnormale danke, gevoel van angs, onvanpaste gedrag, tekort aan belangstelling, abnormaal gelukkige bui, gereelde bui veranderings, probleme met spraak, verlies aan beheer van liggaamℓike bewegings, verlies van sensitiwiteit vir aanraking
- abnormale visie, onduidelike visie
- suising in die ore en 'n draaigevoel (vertigo)
- hartkloppings (vinnige ongereelde aksie van die hart), toename in die harttempo
- asma, kortademheid, hoes, loperige of verstopte neus, sinusitis, borsinfeksie
- smaakversteurings, sooibrand
- inflammasie van die pankreas (erge buikpyn)
- korwe, ekseem, verlies van hare, aknee, velafskilming, infeksie van die haarfollikels, allergiese velreaksie teen sonlig
- gewrigspyn, afbreek van spiere, spierpyn of swakheid, rugpyn, borspyn, versagting van die been (met beenpyn en soms tot frakture)
- Impotensie (verlies aan manlike seksuele funksionering) toename en afname in seksdrang (libido), borsvergroting in mans
- flou, alkohol onverdraagsaamheid, hittegloede, griepagtige simptome
- bloed in die urien, inflammasie van die niere, dikwelse urinering en dorstigheid
- verandering in die vorm van en plek van liggaamsvet (veral in u arms, bene, gesig, nek, borste en middel)
- verhoogde sweet, koors.

Bloedtoetse kan ook die volgende aandui:
- afname van fosfaatvlakke in die bloed
- toename in die vlakke van kreatienkinase in die bloed wat tot spierpyn en swakheid kan lei.
- anemie (lae rooibloedseltelling)
- lae witbloedseltelling ('n laer witbloedseltelling kan veroorsaak dat u meer tot infeksies neig)
- toename in vetsuur- (trigliseriede), bilirubien- of suikervlakke in die bloed
- probleme met die lewer of pankreas
- afname in kalium in die bloed
- toename in kreatinien in die bloed
- proteïene in die urien.

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

OPBERGING EN WEGDOEN VAN TRIEMTA TABLETS
Bewaar by of benede 25 °C (kamertemperatuur). Beskerm teen lig en vogtigheid.
Hou HDPE houers dig toe.
BERG ALLE MEDISYNE BUITE BEREIK VAN KINDERS.

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

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

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

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