TYRICTEN
P1519793

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PROFESSIONAL INFORMATION

NOVAGEN PHARMA

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

TYRICTEN 200/300 mg (Tablet)

COMPOSITION

Each **TYRICTEN 200/300 mg** film-coated tablet contains 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate (which is equivalent to 245 mg tenofovir disoproxil).

Excipients: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and Opadry II White 32K18425 IH (hypromellose, lactose monohydrate, titanium dioxide (C.I. No: 77891), and triacetin).

Contains sugar: Lactose monohydrate 92,2 mg.

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE "WARNINGS AND SPECIAL PRECAUTIONS").

TYRICTEN 200/300 mg IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TYRICTEN 200/300 mg 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 (200 mg) OR TENOFOVIR.

HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE TYRICTEN 200/300 mg, AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE "WARNINGS AND SPECIAL PRECAUTIONS").

TYRICTEN 200/300 mg USED FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) MUST ONLY BE PRESCRIBED TO INDIVIDUALS CONFIRMED TO BE HIV-NEGATIVE IMMEDIATELY PRIOR TO INITIATING AND PERIODICALLY (AT LEAST ONCE EVERY 3 MONTHS) DURING USE. RESISTANT HIV-1 VARIANTS HAVE BEEN IDENTIFIED WITH USE OF TYRICTEN 200/300 mg FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) FOLLOWING UNDETECTED ACUTE HIV-1 INFECTION.

DO NOT INITIATE TYRICTEN 200/300 mg FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) IF SIGNS OR SYMPTOMS OF ACUTE HIV-1 INFECTION ARE PRESENT, UNLESS NEGATIVE INFECTION STATUS IS CONFIRMED (SEE "WARNINGS AND SPECIAL PRECAUTIONS").

PHARMACOLOGICAL CLASSIFICATION

A 20.2.8 Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Emtricitabine: Emtricitabine is a NRTI (Nucleoside and Nucleotide reverse transcriptase inhibitor), which is synthetic nucleoside analogue of cytidine. It is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

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

Resistance:

Emtricitabine: Emtricitabine-resistant isolates of HIV have been selected *in vitro*.

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

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV RT gene.

Tenofovir disoproxil fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in RT and showed a 2 to 4 fold reduction in susceptibility to tenofovir.

Tenofovir-resistant isolates of HIV-1 have also been recovered from some patients treated with tenofovir in combination with certain antiretroviral agents. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution.

iPrEx Trial: In a clinical study of HIV-1 seronegative men who have sex with men, no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 48 subjects in the emtricitabine and tenofovir DF group and 83 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be HIV-1 infected at time of enrolment. The M184V/I substitutions associated with resistance to emtricitabine were observed in 3 of the 10 subjects (2 of 2 in the emtricitabine/tenofovir DF group and 1 of 8 in the placebo group) who were HIV-1 positive at time of enrolment. One of the two subjects in the emtricitabine/tenofovir DF group harboured wild type virus at enrolment and developed the M184V substitution 4 weeks after enrolment. The other subject had indeterminate resistance at enrolment but was found to have the M184I substitution 4 weeks after enrolment.

Partners PrEP Trial: In a clinical study of HIV-1 seronegative partners of heterosexual couples of whom one of the partners was HIV-1 infected, no variants expressing amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 12 subjects in the emtricitabine/tenofovir DF group, 15 subjects in the tenofovir DF group, and 51 subjects in the placebo group. Fourteen subjects were observed to be HIV-1 infected at the time of enrolment (3 in the emtricitabine/tenofovir DF group, 5 in the tenofovir DF group, and 6 in the placebo group). One of the three subjects in the emtricitabine/tenofovir DF group who was infected with wild type virus at enrolment selected an M184V expressing virus by week 12. Two of the five subjects in the tenofovir DF group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at enrolment developed a K65R substitution by week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions upon seroconversion at week 60, although baseline virus was not genotyped and it is unclear if the resistance emerged or was transmitted. Following enrolment, 4 subjects (2 in the tenofovir DF group, 1 in the emtricitabine/tenofovir DF group, and 1 in the placebo group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to non-nucleoside reverse transcriptase inhibitors but have not been associated with tenofovir or emtricitabine and may have been present in the infecting virus.

Cross-resistance:

Emtricitabine and tenofovir disoproxil fumarate: Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognized. The M184V/I and/or K65R substitutions selected *in vitro* by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours either or both of these amino acid substitutions.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine. Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harbouring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir disoproxil fumarate: Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Antiviral Activity:

Emtricitabine and tenofovir disoproxil fumarate: In combination studies evaluating the *in vitro* antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

Emtricitabine: The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. In medicine combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these medicine combinations have not been studied in humans. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, and G and showed strain specific activity against HIV-2.

Tenofovir disoproxil fumarate: The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. In medicine combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G and O.

Pharmacokinetic properties:

Pharmacokinetics in adults:

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarised in Table 1. Emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose, following oral administration of emtricitabine (200 mg). *In vitro* binding of emtricitabine to human plasma proteins is < 4 % and is independent of concentration over the range of 0,02 to 200 µg/ml. Following administration of radiolabelled emtricitabine, approximately 86 % is recovered in the urine and 13 % is recovered as metabolites. The metabolites of emtricitabine include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of active tubular secretion and glomerular filtration. 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. Following oral administration of tenofovir, maximum tenofovir serum concentrations are achieved in 1,0 ± 0,4 hour. *In vitro* binding of tenofovir to human plasma proteins is < 0,7 % and is independent of concentration over the range of 0,01 to 25 µg/ml. Approximately 70 to 80 % of the intravenous dose of tenofovir is recovered as unchanged medicine in the urine. Tenofovir is eliminated by a combination of active tubular secretion and glomerular filtration. Following a single oral dose of tenofovir DF, the terminal elimination half-life is approximately 17 hours.

Table 1:

Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults[1]

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability[2] (%)	92 (83,1 to 106,4)	25 (NC to 45,0)
Plasma Terminal Elimination Half-Life[2] (hr)	10 (7,4 to 18,0)	17 (12,0 to 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:

The combination tablet may be administered with or without food. Administration of the combination tablet following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0,75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35 % and 15 %, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy studies, tenofovir was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when the combination tablet was administered with either a high fat or a light meal.

Special populations:

Race

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of emtricitabine (200 mg).

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

Paediatric patients:

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in children (< 12 years weighing less than 35 kg) (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Geriatric patients:

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in the elderly (> 65 years) (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Patients with impaired renal function:

The pharmacokinetics of emtricitabine and tenofovir are altered in patients with renal impairment (see **"CONTRAINDICATIONS"**, **"WARNINGS AND SPECIAL PRECAUTIONS"**, **"Renal Impairment"**). In patients with creatinine clearance < 50 ml/min, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were significantly increased.

TYRICTEN 200/300 mg should not be used in patients with creatinine clearance < 50 ml/min or in patients with end-stage renal disease requiring dialysis (see **"CONTRAINDICATIONS"**, **"WARNINGS AND SPECIAL PRECAUTIONS"**, **"Renal Impairment"**).

Do not use **TYRICTEN 200/300 mg** for a Pre-exposure Prophylaxis (PrEP) indication in HIV-1 uninfected individuals with a creatinine clearance < 60 ml/min (see **"CONTRAINDICATIONS"**, **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Patients with hepatic impairment:

The pharmacokinetics of tenofovir following a 300 mg dose of tenofovir disoproxil fumarate have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. In patients with hepatic impairment, the pharmacokinetics of the combination tablet or emtricitabine has not been studied. However, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

INDICATIONS

TYRICTEN 200/300 mg is indicated in combination with other antiretroviral agents (such as protease inhibitors or non-nucleoside reverse transcriptase inhibitors) for the treatment of HIV-1 infection in adults.

TYRICTEN 200/300 mg is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) in proven HIV-1 uninfected adults to reduce the risk of sexually acquired HIV-1 in adults at high risk, provided maximum treatment compliance can be monitored.

CONTRAINDICATIONS

TYRICTEN 200/300 mg is contraindicated in:

- Patients with previously demonstrated hypersensitivity to any of the components of **TYRICTEN 200/300 mg**.
- Creatinine CL < 60 ml/min when used for HIV PrEP.
- Creatinine CL < 50 ml/min when used for the treatment of HIV-1.
- Pregnancy and lactation (see **"HUMAN REPRODUCTION"**).

TYRICTEN 200/300 mg should not be co-administered with other tenofovir-containing products, or with other emtricitabine-containing products. **TYRICTEN 200/300 mg** should not be administered with lamivudine containing products due to similarities between emtricitabine and lamivudine.

TYRICTEN 200/300 mg should not be used for Pre-Exposure Prophylaxis (PrEP) in individuals with unknown or positive HIV-1 status.

TYRICTEN 200/300 mg should not be used for PrEP in individuals not fully committed to full treatment compliance.

WARNINGS AND SPECIAL PRECAUTIONS

There are no study results demonstrating the effect of **TYRICTEN 200/300 mg** on clinical progression of HIV-1.

It is not recommended that **TYRICTEN 200/300 mg** be used as a component of a triple nucleoside regimen.

Individuals should be warned that full compliance with treatment is essential to the efficacy in preventing HIV-1 transmission and should be fully informed about the use of other preventative measures including barrier contraception (condoms).

Individuals not fully committed or trusted to be treatment-compliant should not use **TYRICTEN 200/300 mg** for HIV-1 transmission prophylaxis.

Lactic acidosis/Severe hepatomegaly with steatosis:

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues such as **TYRICTEN 200/300 mg** alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogues such as **TYRICTEN 200/300 mg** to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with **TYRICTEN 200/300 mg** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Lactic acidosis/Hyperlactataemia:

Use of **TYRICTEN 200/300 mg** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.

Clinical features are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. In patients with suspicious symptoms or biochemistry, venous lactate level (normal < 2 mmol/l) and serum bicarbonate should be determined and responded to as follows:

Lactate 2 to 5 mmol/l with minimum symptoms: switch to medicines that are less likely to cause lactic acidosis.

Lactate 5 to 10 mmol/l with symptoms and/or with reduced standard bicarbonate: STOP **TYRICTEN 200/300 mg** 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, thyroxicosis, 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 **TYRICTEN 200/300 mg** to patients with known risk factors for liver disease.

Treatment with **TYRICTEN 200/300 mg** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Pancreatitis:

Pancreatitis has been observed in patients receiving **TYRICTEN 200/300 mg.**

Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **TYRICTEN 200/300 mg** until diagnosis of pancreatitis is excluded.

Liver disease:

Use of **TYRICTEN 200/300 mg** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **TYRICTEN 200/300 mg** has not been established in patients with significant underlying liver disorders/diseases.

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.

In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package leaflets for these medicines.

Mitochondrial dysfunction:

Nucleoside and nucleotide analogues such as **TYRICTEN 200/300 mg** 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 and symptoms.

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

All patients with HIV should be tested for the presence of chronic hepatitis B virus (HBV) before initiating **TYRICTEN 200/300 mg** therapy. 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).

TYRICTEN 200/300 mg is not indicated for the treatment of chronic HBV infection and the safety and efficacy of **TYRICTEN 200/300 mg** have not been established in patients co-infected with HBV and HIV.

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

Patients co-infected with HIV and HBV who discontinue **TYRICTEN 200/300 mg** should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are co-infected with HIV and HBV and discontinue **TYRICTEN 200/300 mg**. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal Impairment:

Emtricitabine and tenofovir are principally eliminated by the kidney.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir (see **"SIDE EFFECTS"** and **"CONTRAINDICATIONS"**)

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with **TYRICTEN 200/300 mg**. Routine monitoring of calculated creatinine clearance and serum phosphorous should be performed in patients at risk for renal impairment (see **"CONTRAINDICATIONS"**).

TYRICTEN 200/300 mg should be avoided with concurrent or recent use of a nephrotoxic agent.

TYRICTEN 200/300 mg should not be administered to patients with creatinine clearance below 50 ml/min or patients requiring haemodialysis or for pre-exposure prophylaxis in patients with creatinine clearance below 60 ml/min (see **"CONTRAINDICATIONS"**).

If a decrease in creatinine clearance develops in uninfected individuals using **TYRICTEN 200/300 mg** for PrEP, **TYRICTEN 200/300 mg** should be discontinued (see **"CONTRAINDICATIONS"**).

Patients with moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of **TYRICTEN 200/300 mg** is increased due to decreased clearance. **TYRICTEN 200/300 mg** should therefore not be used in these patients (see **"CONTRAINDICATIONS"**).

Warnings and special precautions regarding interactions:

TYRICTEN 200/300 mg should not be co-administered with additional emtricitabine or tenofovir (see **"CONTRAINDICATIONS"**).

Lamivudine:

Due to similarities between emtricitabine and lamivudine, **TYRICTEN 200/300 mg** should not be co-administered with other medicines containing lamivudine, including lamivudine and zidovudine co-formulation, lamivudine for HIV, lamivudine for HBV, abacavir sulphate and lamivudine co-formulation or abacavir sulphate, lamivudine and zidovudine co-formulation (see **"CONTRAINDICATIONS"**).

Didanosine:

When tenofovir disoproxil fumarate was administered with didanosine the C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy.

In adults weighing > 60 kg, the didanosine dose should be reduced to 250 mg when it is co-administered with **TYRICTEN 200/300 mg**. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg. When co-administered, **TYRICTEN 200/300 mg** and didanosine may be taken under fasted conditions or with a light meal (< 400 kcal, 20 % fat).

Co-administration of didanosine buffered tablet formulation with **TYRICTEN 200/300 mg** should be under fasted conditions (see **"INTERACTIONS"**). Co-administration of **TYRICTEN 200/300 mg** 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 (see **"SIDE EFFECTS"**).

Atazanavir and lopinavir/ritonavir:

This combination has been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown.

Patients receiving atazanavir and lopinavir/ritonavir and **TYRICTEN 200/300 mg** should be monitored for **TYRICTEN 200/300 mg**-associated adverse events and **TYRICTEN 200/300 mg** should be discontinued in patients who develop **TYRICTEN 200/300 mg**-associated adverse events (see **"SIDE EFFECTS"**).

Tenofovir decreases the AUC and C_{min} of atazanavir (see **"INTERACTIONS"**).

When co-administered with **TYRICTEN 200/300 mg**, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg.

Atazanavir without ritonavir should not be co-administered with **TYRICTEN 200/300 mg**.

Renally Excreted Medicines:

Emtricitabine and tenofovir disoproxil fumarate:

Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of **TYRICTEN 200/300 mg** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated substances (see **"INTERACTIONS"**). Some examples include, but are not limited to adefovir dipivoxil, cidofovir, aciclovir, valaciclovir, ganciclovir and valganciclovir.

Tacrolimus can affect renal function. Close monitoring is therefore recommended when it is co-administered with **TYRICTEN 200/300 mg** (see **"INTERACTIONS"**).

Bone Effects:

Bone mineral density:

Tenofovir disoproxil fumarate:

Tenofovir combination therapy is associated with decreased bone mineral density

During therapy with **TYRICTEN 200/300 mg** assessment of bone mineral density (BMD) should be considered for patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. The effect of supplementation with calcium and vitamin D was not studied. If bone abnormalities are suspected then appropriate consultation should be obtained. Bone mineral density monitoring should be considered for HIV infected patients who have a history of pathological bone fracture or are at risk for osteopenia.

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were also observed. In a pre-exposure trial of men having sex with men (MSM), a sub study of 503 subjects found mean changes from baseline in BMD ranging from -0,4 % to -1,0 % across total hip, spine, femoral neck, and trochanter in the emtricitabine/tenofovir disoproxil combination group compared with the placebo group. Bone fractures were reported in 1,7 % of the emtricitabine/tenofovir disoproxil combination group compared with 1,4 % in the placebo group. No correlation between BMD and fractures was noted. A pre-exposure study in heterosexual couples where one of the partners was HIV-1 infected, found similar fracture rates between treatment and placebo groups (0,8 % and 0,6 %, respectively). No BMD evaluations were conducted during this trial. Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir DF, such as contained in **TYRICTEN 200/300 mg** (see **"SIDE EFFECTS"**).

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 Anti-Retroviral Therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Lipodystrophy and metabolic abnormalities:

TYRICTEN 200/300 mg 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, elevated serum lipid and glucose levels in HIV patients, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy, such as **TYRICTEN 200/300 mg.**

The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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 such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are pulmonary tuberculosis, cytomegalovirus retinitis, *Pneumocystis jirovecii* pneumonia (PCP), cryptococcal meningitis and other forms of tuberculosis and atypical myco-bacterial infections.

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.

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including **TYRICTEN 200/300 mg**. During the initial phase of **TYRICTEN 200/300 mg** treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections which may necessitate further evaluation and treatment.

Opportunistic infections:

Patients receiving **TYRICTEN 200/300 mg** 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 **TYRICTEN 200/300 mg**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Comprehensive management to reduce the risk of acquiring HIV-1:

Use **TYRICTEN 200/300 mg** for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because **TYRICTEN 200/300 mg** is not always effective in preventing the acquisition of HIV-1.

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhoea).
- Inform uninfected individuals about and support their efforts in reducing sexual risk behaviour.

Use TYRICTEN 200/300 mg to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV- negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only TYRICTEN 200/300 mg, because TYRICTEN 200/300 mg alone does not constitute a complete treatment regimen for HIV-1 treatment. Therefore, care should be taken to avoid TYRICTEN 200/300 mg exposure in HIV-infected individuals (see "CONTRAINDICATIONS").

- **Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating TYRICTEN 200/300 mg for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g. fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g. unprotected sex, or condom broken during sex with an HIV-1 infected partner) that may have occurred within the last month.**
- **If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use an approved test as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.**
- **While using TYRICTEN 200/300 mg for a PrEP indication, HIV-1 screening tests should be repeated at least once every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using an approved test as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.**

Counsel uninfected individuals to strictly adhere to the recommended **TYRICTEN 200/300 mg** dosing schedule.

The effectiveness of **TYRICTEN 200/300 mg** in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable medicine levels in clinical trials.

Early virologic failure:

Clinical trials in HIV-1 infected patients have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTIs) are generally less effective than regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or an HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported.

Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilising a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

Paediatric Use:

Safety and effectiveness in paediatric patients have not been established.

Geriatric Use:

In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other medicine therapy.

Effects on ability to drive and use machines:

No studies on the effects of either tenofovir disoproxil fumarate or emtricitabine on the ability to drive and use machines have been performed. However dizziness has been reported during treatment with both tenofovir disoproxil fumarate and emtricitabine. Patients should not drive and use machines until they have determined how they are affected.

Lactose warning:

TYRICTEN 200/300 mg contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency glucose-galactose malabsorption or fructose intolerance should not take **TYRICTEN 200/300 mg**.

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS

TYRICTEN 200/300 mg:

No interaction studies have been conducted using **TYRICTEN 200/300 mg**.

The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together versus each agent dosed alone.

In vitro and clinical pharmacokinetic medicine interaction studies have shown the potential for CYP450 mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No medicine interactions due to competition for renal excretion have been observed; however, co-administration of **TYRICTEN 200/300 mg** with medicines that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the co-administered medicine.

Medicines that decrease renal function may increase concentrations of emtricitabine and/or tenofovir. No clinically significant medicine interactions have been observed between emtricitabine and famciclovir, indinavir, zidovudine, stavudine, and tenofovir disoproxil fumarate (see Tables 2 and 3). Similarly, no clinically significant interactions have been observed between tenofovir disoproxil fumarate and abacavir, adefovir dipivoxil, ribavirin, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, and saquinavir/ritonavir in studies conducted in healthy volunteers (see Tables 4 and 5).

Table 2:

Medicine interactions: Changes in pharmacokinetic parameters for emtricitabine in the presence of the co-administered medicine[1]

Co-administered medicine	Dose of co-administered medicine (mg)	Emtricitabine Dose (mg)	N	% Change of emtricitabine pharmacokinetic parameters[2] (90 % CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	↑20 (↑12 to ↑29)
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable.

Table 3:

Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of emtricitabine[1]

Co-administered medicine	Dose of co-administered medicine (mg)	Emtricitabine Dose (mg)	N	% Change of emtricitabine pharmacokinetic parameters[2] (90 % CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	⇔	⇔	⇔
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↑17 (↑0 to ↑38)	↑13 (↑5 to ↑20)	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	NA
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	NA
Stavudine	40 x 1	200 x 1	6	⇔	⇔	NA

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable.

Table 4:

Medicine interactions: Changes in pharmacokinetic parameters for tenofovir[1] in the presence of the co-administered medicine.

Co- administered medicine	Dose of co- administered medicine (mg)	N	% Change of tenofovir pharmacokinetic parameters[2] (90 % CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC
Adefovir dipivoxil	10 once	22	⇔	⇔	NC
Atazanavir[3]	400 once daily x 14 days	33	↑14 (↑8 to ↑20)	↑24 (↑21 to ↑28)	↑22 (↑15 to ↑30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily x 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily x 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily x 7 days	13	↑14 (↓3 to ↑33)	⇔	⇔
Lamivudine	150 twice daily x 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	⇔	↑32 (↑25 to ↑38)	↑51 (↑37 to ↑66)
Nelfinavir	1 250 twice daily X 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1 000/100 twice daily x 14 days	35	⇔	⇔	↑23 (↑16 to ↑30)

1. Patients received tenofovir DF 300 mg once daily.
2. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated.
3. Reyataz South African Prescribing Information (Bristol-Myers Squibb).

Table 5:

Medicine interactions: Changes in pharmacokinetic parameters for co-administered medicine in the presence of tenofovir.

Co- administered medicine	Dose of co- administered medicine (mg)	N	% Change of co-administered medicine pharmacokinetic parameters[1] (90 % CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑12 (↓1 to 26)	⇔	NA
Adefovir dipivoxil	10 once	22	⇔	⇔	NA
Atazanavir[2]	400 once daily x 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir[2]	Atazanavir/ Ritonavir 300/100 once daily x 42 days	10	↓28 (↓50 to ↑5)	↓25[3] (↓42 to ↓3)	↓23[3] (↓46 to ↑10)
Efavirenz	600 once daily x 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily x 7 days	17	⇔	⇔	↑20 (↑12 to ↑29)
Indinavir	800 three times daily x 7 days	12	↓11 (↓30 to ↑12)	⇔	⇔
Lamivudine	150 twice daily X 7 days	15	↓24 (↓34 to ↓12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/ Ritonavir 400/100 twice daily x 14 days	24	⇔	⇔	⇔
Methadone[4]	40 to 110 once daily x 14 days[5]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1 250 twice daily x 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔

1. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable.
2. REYATAZ South African Prescribing Information (Bristol-Myers Squibb).
3. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2, 3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
4. R-(active), S-and total methadone exposures were equivalent when dosed alone or with tenofovir DF.
5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
6. Ethinyl estradiol 0,035 mg and 17-deacetyl norgestimate 0,25 mg (pharmacologically active metabolite) exposures were equivalent when dosed alone or with tenofovir DF.
7. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are co-administered.

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

Combinations containing any of the following medications, depending on the amount present, may also interact with **TYRICTEN 200/300 mg**. The medicine interactions described are based on studies conducted using the individual agents.

Abacavir:

Co-administration of abacavir and tenofovir resulted in increase of abacavir C_{max}.

Atazanavir and/or lopinavir/ritonavir:

Concurrent use of atazanavir and **TYRICTEN 200/300 mg** may result in increased concentrations of tenofovir and decreases in the AUC and C_{min} of atazanavir. It is recommended that atazanavir be administered with ritonavir. Atazanavir without ritonavir should not be co-administered with **TYRICTEN 200/300 mg**.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of interaction is unknown. Monitor patients for emtricitabine/tenofovir-associated adverse events and discontinue **TYRICTEN 200/300 mg** in patients who develop these adverse events.

Didanosine:

Co-administration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 6 summarises the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric-coated capsules significantly increase the C_{max} and AUC of didanosine.

When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown.

Table 6:

Medicine interactions: Pharmacokinetic parameters for didanosine in the presence of tenofovir.

Didanosine[1] dose (mg)/Method of administration[2]	Tenofovir method of administration [2]	N	% Difference (90 % CI) vs. didanosine 400 mg alone, fasted[3]	
			C_{max}	AUC
Buffered tablets				
400 once daily[4] x 7 days	Fasted 1 hour after didanosine	14	↑28 (↑11 to ↑48)	↑44 (↑31 to ↑59)
Enteric-coated capsules				
400 once, fasted	With food, 2 hr after didanosine	26	↑48 (↑25 to ↑76)	↑48 (↑31 to ↑67)
400 once, with food	Simultaneously with didanosine	26	↑64 (↑41 to ↑89)	↑60 (↑44 to ↑79)
250 once, fasted	With food, 2 hr after didanosine	28	↓10 (↓22 to ↑3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑14 (0 to ↑31)
250 once, with food	Simultaneously with didanosine	28	↓29 (↓39 to ↓18)	↓11 (↓23 to ↑2)

1. See **"WARNINGS AND SPECIAL PRECAUTIONS"** regarding use of didanosine with tenofovir.
2. Administration with food was with a light meal (~ 373 kcal, 20 % fat).
3. Increase =↑ ; Decrease = ↓; No Difference = ⇔.
4. Includes 4 subjects weighing < 60 kg receiving ddl 250 mg.

Emtricitabine or tenofovir disoproxil fumarate:

TYRICTEN 200/300 mg combination is a fixed-dose product. Additional emtricitabine or tenofovir disoproxil fumarate should not be used with the combination product.

Indinavir:

Concurrent administration of indinavir and tenofovir resulted in an increase of tenofovir C_{max} and a decrease in indinavir C_{max}.

Lamivudine or products containing lamivudine:

Should not be co-administered due to similarities between emtricitabine and lamivudine; also, lamivudine C_{max} is decreased with tenofovir co-administration.

HUMAN REPRODUCTION

Pregnancy:

The safety of **TYRICTEN 200/300 mg** in pregnancy and lactation has not been established.

There are no adequate and well-controlled studies in pregnant women. **TYRICTEN 200/300 mg** should not be used during pregnancy (see **"CONTRAINDICATIONS"**).

A reliable method of contraception should be used to avoid pregnancy while taking **TYRICTEN 200/300 mg**.

Lactation:

HIV-infected mothers should not breastfeed their infants, to avoid risking postnatal transmission of HIV.

Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. It is not known whether emtricitabine is excreted in human milk.

Because of both 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 receiving TYRICTEN 200/300 mg.

DOSAGE AND DIRECTIONS FOR USE

Dosage in adults for treatment of HIV-1 infection:

The dose of **TYRICTEN 200/300 mg** is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Dosage for Pre-Exposure Prophylaxis:

The dose of **TYRICTEN 200/300 mg** in HIV-1 uninfected adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

Significantly increased medicine exposure occurred when **TYRICTEN 200/300 mg** was administered to patients with moderate to severe renal impairment (see **"CONTRAINDICATIONS"**).

Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in all individuals (see **"CONTRAINDICATIONS"**, **"WARNINGS AND SPECIAL PRECAUTIONS"**, **"Renal impairment"**).

SIDE EFFECTS

Side effects reported for TYRICTEN 200/300 mg:

Blood and the lymphatic system disorders:

Frequent: Neutropenia.
Frequency unknown: Anaemia.

Immune system disorders:

Frequent: Allergic reaction, including angioedema.

Metabolism and nutrition disorders:

Frequent: Hypertriglyceridaemia, hyperglycaemia.
Frequency unknown: Hypophosphataemia, lactic acidosis, hypokalaemia.

Psychiatric disorders:

Frequent: Insomnia, abnormal dreams, depression.

Nervous system disorders:

Frequent: Dizziness, headache, neuritis, paraesthesia, peripheral neuropathy.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea, increased cough, rhinitis, chest pain, pneumonia.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, flatulence, dyspepsia, abdominal pain, amylase elevation, lipase elevation.
Frequency unknown: Pancreatitis.

Hepato-biliary disorders:

Frequent: Hyperbilirubinaemia, increased liver enzymes (including increased AST, increased ALT and/or gamma GT).
Frequency unknown: Hepatitis, hepatic steatosis.

Skin and subcutaneous tissue disorders:

Frequent: Rash event (rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash), skin discolouration, hyperpigmentation.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Creatine kinase elevation.
Frequency unknown: Myopathy, osteomalacia (both associated with proximal renal tubulopathy), rhabdomyolysis, muscular weakness.

Renal and urinary disorders:

Frequency unknown: Increased creatinine, renal insufficiency, renal failure, acute renal failure, Fanconi syndrome, proximal tubulopathy, nephrogenic diabetes insipidus, proteinuria, acute tubular necrosis, polyuria, interstitial nephritis (including acute cases).

General disorders and administrative site conditions:

Frequent: Pain, asthenia, fever, sweating, weight loss.

Side effects reported for Emtricitabine (200 mg):

Nervous system disorders:

Frequency unknown: Depressive disorder, neuropathy, peripheral neuritis, paraesthesia.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Arthralgia, myalgia.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Increased cough and rhinitis.

Side effects reported for Tenofovir (300 mg):

Gastrointestinal disorders:

Frequent: Anorexia.

Nervous system disorders:

Frequency unknown: Depression, peripheral neuropathy (including peripheral neuritis and neuropathy), anxiety.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Back pain, myalgia, arthralgia.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Chest pain, pneumonia.

Renal and urinary disorders:

Frequency unknown: Haematuria.

General disorders and administration site conditions:

Frequency unknown: Fever, sweating, weight loss.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In overdose, side effects will be exacerbated and exaggerated.

The patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary, if overdose occurs.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine (200 mg).

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: Limited clinical experience at doses higher than the therapeutic dose of tenofovir 300 mg is available. The effects of higher doses are not known. Tenofovir is poorly removed by haemodialysis. Following a single 300 mg dose of tenofovir DF, a four hour haemodialysis session removed only 10 % of the administered tenofovir dose.

IDENTIFICATION

White to off-white, modified capsule shaped, film-coated tablets, debossed with "I" on one side and "37" on other side.

PRESENTATION

HDPE Container Pack:

Tablets are packed in white opaque round HDPE containers with a 38 mm white opaque polypropylene child resistant closure with a wad having an induction sealing liner, containing one 3 g silica gel sachet.

The HDPE container will be further packed in a pre-printed carton with a package leaflet.

Pack size: 30's - One HDPE container contains 30 tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Keep the container tightly closed.

Do not use if seal over bottle opening is broken or missing.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

44/20.2.8/0086

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

Novagen Pharma (Pty) Ltd
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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

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Date of latest revision of the text as approved by Council: 6 April 2017

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

TYRICTEN 200/300 mg (Emtricitabine/Tenofovir disoproxil fumarate) Tablet

Read all of this leaflet carefully before you start taking TYRICTEN 200/300 mg:

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **TYRICTEN 200/300 mg** 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.

WARNING

TYRICTEN 200/300 mg MAY LEAD TO SERIOUS PROBLEMS WITH YOUR LIVER OR CAUSE TOO MUCH ACID IN YOUR BLOOD. IF LEFT UNTREATED, THIS MAY CAUSE DEATH (SEE "TAKE SPECIAL CARE WITH TYRICTEN 200/300 mg").

TYRICTEN 200/300 mg IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF TYRICTEN 200/300 mg IN PATIENTS WHO ARE INFECTED WITH BOTH HUMAN IMMUNO-DEFICIENCY VIRUS (HIV) AND HEPATITIS B VIRUS (HBV) HAVE NOT BEEN ESTABLISHED. YOU SHOULD BE CLOSELY MONITORED BY YOUR DOCTOR FOR SEVERAL MONTHS IF YOU DISCONTINUE THE USE OF TYRICTEN 200/300 mg AND ARE INFECTED WITH BOTH HBV AND HIV. IF APPROPRIATE, YOUR DOCTOR MAY PRESCRIBE ANTI-HEPATITIS B THERAPY.

TYRICTEN 200/300 mg USED FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) WILL ONLY BE PRESCRIBED TO YOU IF YOU ARE CONFIRMED TO BE HIV-NEGATIVE IMMEDIATELY PRIOR TO INITIATING TYRICTEN 200/300 mg AND AT LEAST ONCE EVERY 3 MONTHS WHILE USING TYRICTEN 200/300 mg.

DO NOT TAKE TYRICTEN 200/300 mg FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) IF YOU HAVE SIGNS OR SYMPTOMS OF ACUTE HIV-1 INFECTION, UNLESS NEGATIVE INFECTION STATUS IS CONFIRMED.

IF YOU ALREADY HAVE HIV OR GET HIV AND TAKE TYRICTEN 200/300 mg FOR PRE-EXPOSURE PROPHYLAXIS (PrEP), THE HIV VIRUS MAY DEVELOP RESISTANCE TO TYRICTEN 200/300 mg AND BECOME MORE DIFFICULT TO TREAT.

1. WHAT TYRICTEN 200/300 mg CONTAINS

The active substances are emtricitabine and tenofovir disoproxil fumarate.

Each film-coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate.

The other ingredients are: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and Opadry II White 32K18425 IH.

The Opadry II White 32K18425 IH contains: Hypromellose, lactose monohydrate, titanium dioxide (C.I. No: 77891), and triacetin.

The tablets contain sugar: Lactose monohydrate 92,2 mg.

Important information about some of the ingredients of TYRICTEN 200/300 mg:

TYRICTEN 200/300 mg contains lactose. Patients with the rare hereditary conditions of lactose or galactose intolerance should not take **TYRICTEN 200/300 mg**.

Lactose may have an effect on the control of your blood sugar if you have diabetes mellitus.

2. WHAT TYRICTEN 200/300 mg IS USED FOR

TYRICTEN 200/300 mg is a type of medicine called an HIV (Human Immunodeficiency Virus) nucleoside analogue reverse transcriptase inhibitor (NRTI). **TYRICTEN 200/300 mg** contains two active substances, emtricitabine (200 mg) and tenofovir disoproxil fumarate (or tenofovir DF) (300 mg), combined in one tablet.

Each of these active substances, also known as antiretroviral medicines, work by interfering with an enzyme (reverse transcriptase) that is essential for the virus to multiply.

TREATMENT WITH TYRICTEN 200/300 mg DOES NOT PREVENT TRANSMISSION OF HIV.

Treatment for HIV infection:

TYRICTEN 200/300 mg is used in adults in combination with other anti-HIV medicines to treat people with HIV infection.

Treatment for Pre-Exposure Prophylaxis (PrEP):

To reduce the risk of getting HIV-1 in adults, **TYRICTEN 200/300 mg** is to be used strictly in combination with safer sex practices and with rigorous use at all times. This is called Pre-Exposure Prophylaxis or PrEP.

3. BEFORE YOU TAKE TYRICTEN 200/300 mg

Do not take TYRICTEN 200/300 mg:

- If you are hypersensitive (allergic) to emtricitabine, tenofovir disoproxil fumarate, or any of the other ingredients of **TYRICTEN 200/300 mg**.
- If you have kidney problems or are on dialysis.
- If you are pregnant or breastfeeding.
- If you are already taking any other tenofovir or emtricitabine containing medicines or medicines containing lamivudine because these medicines contain the same or similar active ingredients.
- If you are a woman who is taking **TYRICTEN 200/300 mg** to prevent HIV infection and you become pregnant while taking **TYRICTEN 200/300 mg.**
- If you are HIV positive or if your HIV status is not known, you should not use **TYRICTEN 200/300 mg** to prevent HIV infection.
- If you are not fully committed to use **TYRICTEN 200/300 mg** every day for Pre-Exposure Prophylaxis.

See the section "WHAT TYRICTEN 200/300 mg IS USED FOR" and talk to your healthcare provider for more information about how to prevent HIV infection.

Take special care with TYRICTEN 200/300 mg:

TYRICTEN 200/300 mg may lead to serious problems with your liver or cause too much acid in your blood. If left untreated, this may cause death. The safety and efficacy of TYRICTEN 200/300 mg in patients who are infected with both human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have not been established. TYRICTEN 200/300 mg should not be used for treatment of chronic HBV infection. You should be closely monitored by your doctor for several months if you are infected with HBV and discontinue the use of TYRICTEN 200/300 mg.

- **TYRICTEN 200/300 mg** may cause lactic acidosis, together with an enlarged liver, which can be fatal. Deep, rapid breathing, drowsiness, and non-specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. Lactic acidosis occurs more often in women, particularly if they are overweight.

Tell your doctor if you have liver disease (including hepatitis B). **TYRICTEN 200/300 mg** should not be used to treat hepatitis B virus infection (HBV; an on-going liver infection). Tell your doctor if you have or think you may have HBV. Your doctor may test you to see if you have HBV before you begin your treatment with **TYRICTEN 200/300 mg**. If you have HBV and you take **TYRICTEN 200/300 mg**, your condition may suddenly worsen when you stop taking **TYRICTEN 200/300 mg.** Your doctor will examine you and order laboratory tests regularly for several months after you stop taking **TYRICTEN 200/300 mg** to see if your HBV has worsened.

Tell your doctor if you have had kidney disease, or if tests have shown problems with your kidneys. **TYRICTEN 200/300 mg** may affect your kidneys. Before starting treatment, your doctor may order blood tests to assess kidney function. Your doctor may also order blood tests during treatment to monitor your kidneys.

- **TYRICTEN 200/300 mg** is not usually taken with other medicines that can damage your kidneys. If this is unavoidable, your doctor will monitor your kidney function.
- Bone problems: Some patients taking combination antiretroviral therapy may develop a bone disease. Your doctor may consider monitoring your bones if you have a history of bone fracture or are at risk for osteopenia (a condition where bone mineral density is lower than normal).
- **TYRICTEN 200/300 mg** may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face; gain fat around the abdomen (tummy) and internal organs; get larger breasts or fatty lumps on the back of the neck (buffalo hump). The cause and the long-term effects of these changes are not yet known.
- **TYRICTEN 200/300 mg** has not been studied in patients over 65 years of age. If you are older than this and prescribed **TYRICTEN 200/300 mg**, your doctor will monitor you carefully.
- The safety and effectiveness of **TYRICTEN 200/300 mg** in children and adolescents has not been determined.
- Any child exposed in their mother's womb to **TYRICTEN 200/300 mg**, even HIV negative children, should have clinical and laboratory follow up and should be fully investigated for possible mitochondrial dysfunction.
- Look out for infections. If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection or inflammation or worsening of the symptoms of an existing infection once treatment with **TYRICTEN 200/300 mg** is started. If you notice signs of inflammation or infection, tell your doctor at once.
- If you are taking other medicines, as **TYRICTEN 200/300 mg** may interact with these other medicines.
- If you are diabetic, overweight or have high cholesterol, talk to your doctor.

Other important information to know before taking TYRICTEN 200/300 mg for HIV-1 treatment:

- You must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.
- **TYRICTEN 200/300 mg does not cure HIV.** If you already have HIV or get HIV and take **TYRICTEN 200/300 mg** by itself without other medicines, you may develop resistance to **TYRICTEN 200/300 mg**. This means that the HIV virus may become harder to treat.
- **TYRICTEN 200/300 mg** does not lower your chance of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safe sex.
- You may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak.

Some of these conditions are different forms of tuberculosis infection, a form of pneumonia, herpes virus infections and a form of meningitis (infection of the protective membranes surrounding the brain and spinal cord).

Other important information to know before taking TYRICTEN 200/300 mg to help prevent you from getting HIV:

- **You must get tested to be sure you are HIV-negative.** It is important that you also get tested at least every 3 months as recommended by your healthcare provider while taking **TYRICTEN 200/300 mg**. Ask your partner to get tested. Know the HIV status of your partner.
- **TYRICTEN 200/300 mg** may not always keep you from getting HIV.
- **You must still practice safe sex at all times. Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **You must also use other prevention methods to keep from getting HIV.**
- Get information and support to help reduce risky sexual behaviour.
- Have fewer sex partners.
- **Do not miss any doses of TYRICTEN 200/300 mg. Missing doses increases your risk of getting HIV.**

Other important information to know before taking TYRICTEN 200/300 mg to help prevent you from getting HIV or for HIV-1 treatment:

Avoid doing things that can increase your risk of spreading HIV infection to other people if you are HIV-infected, or increase your risk of acquiring HIV if you are taking **TYRICTEN 200/300 mg** for prevention.

These include:

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Tell your healthcare provider if you have any of the following symptoms within the last month before you start taking **TYRICTEN 200/300 mg** or at any time while taking **TYRICTEN 200/300 mg**:

- tiredness
- fever
- sweating a lot (especially at night)
- rash
- vomiting
- diarrhoea
- joint or muscle aches
- headache
- sore throat
- enlarged lymph nodes in the neck or groin.

These may be signs of HIV infection and you may need to have another test to diagnose HIV.

Also, tell your healthcare provider if you think you were recently exposed to the HIV virus. If you are already taking **TYRICTEN 200/300 mg** to prevent HIV-1 infection, your healthcare provider may tell you to stop taking **TYRICTEN 200/300 mg** until an HIV test confirms that you do not have HIV-1 infection.

Taking TYRICTEN 200/300 mg with food and drink:

TYRICTEN 200/300 mg can be taken with or without food. Take **TYRICTEN 200/300 mg** at the same time each day.

Pregnancy and Breastfeeding:

- You must not take **TYRICTEN 200/300 mg** during pregnancy. The effects of **TYRICTEN 200/300 mg** on pregnant women or their unborn babies are not known.
- A reliable method of contraception should be used to avoid pregnancy while taking **TYRICTEN 200/300 mg**.
- Do not breastfeed during treatment with **TYRICTEN 200/300 mg**. Do not breastfeed if you have HIV. It is not known whether the active substances in this medicine pass into human breast milk. If you are a woman who has or will have a baby, talk to your healthcare provider about the best way to feed your baby.
- If you are a woman with HIV it is recommended that you do not breastfeed, to avoid passing the virus to the baby in breast milk. If your baby does not already have HIV, there is a chance that the baby can get HIV through breastfeeding.

If you are pregnant or breastfeeding your baby please consult your doctor, pharmacist or other healthcare professional for advice before taking **TYRICTEN 200/300 mg**.

Driving and using machinery:

TYRICTEN 200/300 mg may cause dizziness. Care should be taken and you should not drive or use any tools or machines if you feel dizzy.

Taking other medicines with TYRICTEN 200/300 mg:

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

- You should not take **TYRICTEN 200/300 mg** if you are already taking other medicines that contain emtricitabine, tenofovir disoproxil fumarate or lamivudine. **TYRICTEN 200/300 mg should not be used with those medicines because they contain the same or similar active ingredients as TYRICTEN 200/300 mg (see "DO NOT TAKE TYRICTEN 200/300 mg").**
- Tell your doctor if you are taking atazanavir and/or lopinavir/ritonavir: 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 **TYRICTEN 200/300 mg**.
- Tell your doctor if you are taking other medicines containing didanosine (for HIV infection). Taking **TYRICTEN 200/300 mg** 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.

Tell your doctor if you are taking other medicines that may reduce your kidney function. Some examples include adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

Keep a complete list of all the medicines that you take. Make a new list when medicines are added or stopped. Give copies of this list to all of your healthcare providers and pharmacist every time you visit your healthcare provider or fill a prescription.

4. HOW TO TAKE TYRICTEN 200/300 mg

Do not share medicines prescribed for you with any other person.

Always take **TYRICTEN 200/300 mg** 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 **TYRICTEN 200/300 mg** is too strong or too weak, talk to your doctor or pharmacist.

Recommended dosage of TYRICTEN 200/300 mg:

The usual adult dose is one tablet once a day, taken with or without food. Take **TYRICTEN 200/300 mg** at the same time each day.

Treatment of HIV:

If you take **TYRICTEN 200/300 mg** for the treatment of HIV infection, it should be used in combination with other anti-HIV medicines.

Prevention of HIV:

If you take TYRICTEN 200/300 mg to reduce the risk of getting HIV-1, you must also use other methods to reduce your risk of getting HIV. See "Take special care with TYRICTEN 200/300 mg".

Your doctor will tell you how long your treatment with **TYRICTEN 200/300 mg** will last. Do not stop treatment early.

If you take more TYRICTEN 200/300 mg than you should:

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

If you forget to take TYRICTEN 200/300 mg:

It is important that you do not miss any doses. 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. Contact your healthcare provider or pharmacist if you are not sure what to do. Do not take more than one **TYRICTEN 200/300 mg** in a day.

Effects when treatment with TYRICTEN 200/300 mg is stopped:

You should not stop treatment unless your doctor instructs you to. When your **TYRICTEN 200/300 mg** supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood will increase if the medicine is stopped for even a short time. The virus may develop resistance to **TYRICTEN 200/300 mg** and become difficult to treat.

5. POSSIBLE SIDE EFFECTS

TYRICTEN 200/300 mg can have side effects.

Not all side effects reported for **TYRICTEN 200/300 mg** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **TYRICTEN 200/300 mg**, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop taking TYRICTEN 200/300 mg and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing of breathing (angioedema);
- rash or itching;
- fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **TYRICTEN 200/300 mg**. 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:

- Difficulty breathing;
- less urine than is normal for you;
- signs or symptoms of lactic acidosis (build-up of acid in the blood) e.g. feeling weak or tired, having unusual muscle pain, trouble breathing, stomach pain with nausea and vomiting, feeling cold (especially in your arms and legs), feeling dizzy and lightheaded and having a fast or irregular heartbeat;
- signs or symptoms of serious liver problems e.g. skin or white part of the eye turns yellow (jaundice), urine turns dark, stools turn light in colour, feeling sick to your stomach (nausea), have lower stomach area pain (abdominal pain) and not feeling like eating food for several days or longer;
- signs of softening of the bones (bone pain and sometimes resulting in fractures).

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

Tell your doctor if you notice any of the following:

The following side effects have been frequently reported:

- Stomach pain;
- pain;
- abnormal physical weakness or lack of energy;
- diarrhoea;
- headache;
- pins and needles; inflammation of the nerves causing pain;
- increased cough; runny nose; pneumonia (lung infection);
- chest pain;
- nausea (feeling sick), vomiting;
- dizziness;
- difficulty sleeping, abnormal dreams; depressed mood;
- problems with digestion resulting in discomfort after meals, feeling bloated, flatulence;
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin which may be allergic reactions), itching, changes in skin colour including darkening of the skin in patches;
- other allergic reactions e.g. wheezing, swelling or feeling lightheaded;
- fever, sweating, weight loss;
- eating disorder.

Blood tests may also show:

- Low white blood cell count (a reduced white blood cell count can make you more prone to infection);
- increased triglycerides (fatty acids), bile or sugar in the blood;
- increased creatine kinase (an enzyme resulting from breakdown of your muscles);
- increased amylase or lipase in the blood;
- increased liver enzymes.

The following side effects have been reported with unknown frequency:

- Back pain caused by kidney problems;
- anaemia (low red blood cell count), which may include symptoms e.g. fatigue, skin pallor, shortness of breath, light-headedness, dizziness, or a fast heartbeat;
- breakdown of muscle, muscle pain or weakness which may occur due to damage to the kidney tubule cells;
- inflammation of the pancreas which most commonly begins with abdominal pain in the middle or upper left part of the abdomen and may increase after eating or lying flat on the back.

Blood and urine tests may also show:

- Decreases in potassium in the blood;
- decreases in phosphate in the blood;
- increased creatinine in your blood;
- changes to your urine.

This list of side effects is not complete. If you have questions about side effects, ask your healthcare provider. You should report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF TYRICTEN 200/300 mg

Store at or below 30 °C (room temperature). Keep the container tightly closed.

Do not use if seal over bottle opening is broken or missing.

STORE 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).

7. PRESENTATION OF TYRICTEN 200/300 mg

HDPE Container Pack:

Tablets are packed in white opaque round HDPE containers with a 38 mm white opaque polypropylene child resistant closure with a wad having an induction sealing liner, containing one 3 g silica gel sachet.

The HDPE container will be further packed in a pre-printed carton with a package leaflet.

Pack size: 30's - One HDPE container contains 30 tablets.

8. IDENTIFICATION OF TYRICTEN 200/300 mg

White to off-white, modified capsule shaped, film-coated tablets, debossed with "I" on one side and "37" on other side.

9. REGISTRATION NUMBER

44/20.2.8/0086

10. NAME, BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd
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11. DATE OF PUBLICATION OF THIS PATIENT INFORMATION LEAFLET

Date of registration: 12 September 2012
Date of notification with regard to amended Reg. 9 and 10: 2 February 2015
Date of latest revision of the text as approved by Council: 6 April 2017

PROFESSIONELE INLIGTING

NOVAGEN
PHARMA

SKEDULERINGSTATUS

S4

EIENDOMSNAAM EN DOSEERVORM

TYRICTEN 200/300 mg (Tablet)

SAMESTELLING

Elke **TYRICTEN 200/300 mg** filmbedekte tablet bevat 200 mg emtrisitabien en 300 mg tenofovirdisoproksielfumaraat (wat ekwivalent is aan 245 mg tenofovirdisoproksiel).

Eksipiënte: Natriumkroskarmellose, laktosemonohidraat, magnesiumstearaat, mikrokristallyne sellulose, pre-gelatineerde stysel en Opadry II Wit 32K18425 IH (hipromellose, laktosemonohidraat, titaandioksied (C.I.No: 77891), en triasetien).

Bevat suiker: Laktosemonohidraat 92,2 mg.

WAARSKUWING

MELKSUURASIDOSE EN ERGE HEPATOMEGALIE MET STEATOSE, WAARONDER STERFGEVALLE, IS MET DIE GEBRUIK VAN NUKLEOSIEDANALOË, ALLEEN OF IN KOMBINASIE MET ANTIRETROVIRALE MIDDELS AANGEMELD (SIEN "WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS").

TYRICTEN 200/300 mg WORD NIE VIR DIE BEHANDELING VAN CHRONIESE HEPATITIS B-VIRUS (HBV) AANGEDUI NIE EN DIE VEILIGHEID EN DOELTREFFENDHEID VAN TYRICTEN 200/300 mg IS NIE BY PASIËNTE WAT BEIDE MET HBV EN MIV BESMET IS, VASGESTEL NIE. ERGE AKUTE VERERGERING VAN HEPATITIS B IS BY PASIËNTE WAT DIE GEBRUIK VAN EMTRISITABIEN (200 mg) OF TENOFOVIR GESTAAK HET, AANGEMELD.

LEWERFUNKSIE MOET NOUKEURIG GEMONITEER WORD, DEUR BEIDE KLINIESE EN LABORATORIUMOPVOLGING, VIR TEN MINSTE VERSKEIE MAANDE BY PASIËNTE WAT TYRICTEN 200/300 mg GESTAAK HET EN WAT MET BEIDE MIV EN HBV GEÏNFEKTEER IS. INDIEN VAN TOEPASSING KAN DIE INSTELLING VAN ANTI-HEPATITIS B BEHANDELING GEREGVERDIG WEES (SIEN "WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS").

TYRICTEN 200/300 mg GEBRUIK VIR PRE-BLOOTSTELLING PROFILAKSE (PrEP) MOET SLEGS VOORGESKRYF WORD AAN INDIVIDUE WAT ONMIDDELLIK VOOR DIE INISIËRING EN PERIODIEK TYDENS GEBRUIK (TEN MINSTE EEN KEER ELKE 3 MAANDE) MIV-NEGATIEF IS EN DIT BEVESTIG IS. WEERSTANDIGE MIV-1 VARIANTE IS GEÏDENTIFISEER MET DIE GEBRUIK VAN TYRICTEN 200/300 mg VIR PRE-BLOOTSTELLING PROFILAKSE (PrEP) NA AKUTE MIV-1 INFEKSIE WAT NIE OPGEMERK WAS NIE.

MOENIE TYRICTEN 200/300 mg INISIEER VIR PRE-BLOOTSTELLING PROFILAKSE (PrEP) NIE, INDIEN TEKENS OF SIMPTOME VAN AKUTE MIV-1 INFEKSIE TEENWOORDIG IS NIE, TENSY 'N NEGATIEWE INFEKSIESTATUS BEVESTIG IS (SIEN "WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS").

FARMAKOLOGIESE KLASSIFIKASIE

A 20.2.8 Antimikrobiese (chemoterapeutiese) middels. Virusteenmiddels.

FARMAKOLOGIESE WERKING

Farmakodinamiese eienskappe:

Emtrisitabien: Emtrisitabien is 'n NRTI (nukleosied- en nukleotied-trutranskriptaseremmer), wat 'n sintetiese nukleosiedanaloog van sitidien is. Dit word deur sellulêre ensieme gefosforileer om emtrisitabien 5'-trifosfaat te vorm. Emtrisitabien 5'-trifosfaat inhibeer die aktiwiteit van MIV-1 trutranskriptase (TT), deur met die natuurlike substraat deoksisitidien 5'-trifosfaat te kompeteer en deur in die groeiende virus-DNA geïnkorporeer te word, wat tot beëindiging van die ketting lei. Emtrisitabien 5'-trifosfaat is 'n swak inhibeerder van DNS-polimerase α, β, ε en mitochondriese DNS-polimerase □ in soogdiere.

Tenofovirdisoproksielfumaraat: Tenofovirdisoproksielfumaraat, ook bekend as tenofovir DF, is 'n NRTI (nukleosied- en nukleotied-trutranskriptaseremmer). Dit is 'n asikliese nukleosiedfosfonaat diëster analoog van adenosienmonofosfaat. Tenofovirdisoproksielfumaraat benodig aanvanklike hidrolise van die diëster vir omskakeling van tenofovir en daaropvolgende fosforilerings deur sellulêre ensieme om tenofovirdifosfaat te vorm. Tenofovirdifosfaat rem die werking van MIV-1 trutranskriptase deur te kompeteer met die natuurlike substraat deoksiadenosien 5'-trifosfaat en na invoeging in DNS word die DNS-ketting getermineer. Tenofovirdifosfaat is 'n swak remmer van DNS-polimerase-α, -β en mitochondriese DNS-polimerase-γ by soogdiere.

Weerstandigheid:

Emtrisitabien: Emtrisitabien-weerstandbiedende isolate van MIV is *in vitro* geselekteer.

Genotipiese analise van hierdie isolate het getoon dat verminderde vatbaarheid vir emtrisitabien met 'n mutasie in die MIV trutranskriptase geen by kodon-184 geassosieer kan word, met die gevolglike aminosuur substitusie van metionien met valien of isoleusien (M184V/I).

MIV-isolate weerstandig teen emtrisitabien is ook geïdentifiseer by sommige pasiënte wat behandeling met emtrisitabien alleen of in kombinasie met ander antiretrovirale middels ontvang het. Genotipiese analise van hierdie isolate het getoon dat die weerstandigheid deur M184V/I mutasies in die MIV trutranskriptase geen veroorsaak is.

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

Tenofovir-weerstandbiedende stamme van MIV-1 is ook by sommige pasiënte wat tenofovir in kombinasie met sekere antiretrovirale middels ontvang het, geïsoleer. Genotipiese analise van die weerstandige isolate het 'n mutasie in die MIV-1 trutranskriptase geen getoon, wat tot die K65R aminosuur substitusie lei.

iPrEx-Studie: In 'n kliniese studie van MIV-1 seronegatiewe mans, wat seks gehad het met mans, was geen substitusies van aminosuur geassosieer met weerstandigheid teen emtrisitabien of tenofovir ten tye van serokonversie onder die 48 proefpersone in die emtrisitabien en tenofovir DF-groep en 83 proefpersone in die plasebogroep, wat tydens die studie met MIV-1 besmet geraak het nie. Daar was tien proefpersone waargeneem wat ten tye van die registrasie met MIV-1 besmet was. Die M184V/I substitusies wat met weerstandigheid teen emtrisitabien geassosieer word, is by 3 van die 10 proefpersone (2 uit 2 in die emtrisitabien/tenofovir DF-groep en 1 van 8 in die plasebogroep) wat MIV-1 positief was ten tye van registrasie, waargeneem. Een van die twee proefpersone in die emtrisitabien/tenofovir DF-groep het by registrasie 'n wildetipe virus gehad en het 4 weke na registrasie die M184V-substitusie ontwikkel. Die ander proefpersoon het onbepaalde weerstand by inskrywing gehad maar het 4 weke na registrasie die M184I-substitusie gehad.

Vennote-PrEP-studie: In 'n kliniese studie van MIV-1 seronegatiewe vennote van heteroseksuele paartjies waarvan een van die vennote met MIV-1 besmet was, was geen variante wat uitdrukking gee aan aminosuur substitusies wat geassosieer word met weerstandigheid teen emtrisitabien of tenofovir ten tye van serokonversie onder 12 proefpersone in die emtrisitabien/ tenofovir DF-groep, 15 proefpersone in die tenofovir DF-groep, en 51 proefpersone in die plasebogroep, waargeneem nie. Veertien proefpersone was met MIV-1 besmet ten tye van die registrasie (3 in die emtrisitabien/ tenofovir DF-groep, 5 in die tenofovir DF-groep, en 6 in die plasebogroep). Een van die drie proefpersone in die emtrisitabien/ tenofovir DF-groep wat by registrasie al met die wildetipe virus besmet was, het teen week 12 'n M184V-uitdrukkende virus geselekteer. Twee van die vyf proefpersone in die tenofovir DF-groep het tenofovir-weerstandige virusse ten tye van serokonversie gehad; een proefpersoon wat besmet was met wildetipe virus by inskrywing, het 'n K65R-substitusie teen week 16 ontwikkel, terwyl die tweede proefpersoon 'n virus gehad het wat die kombinasie van D67N en K70R substitusies na serokonversie teen week 60 gehad het, hoewel basislyn virus nie gegenotipeer was nie en dit nie duidelik was of die weerstandigheid ontstaan het, of oorgedra is nie. Na registrasie het 4 proefpersone (2 in die tenofovir DF-groep, 1 in die emtrisitabien/tenofovir DF-groep en 1 in die plasebogroep) virus-uitdrukking van K103N en V106A substitusies gehad, wat hoëvlak weerstandigheid verleen teen nie-nukleosied trutranskriptaseremmers, maar wat nie met tenofovir of emtrisitabien geassosieer was nie, en wat in die infekterende virus teenwoordig kon wees.

Kruisweerstandigheid:

Emtrisitabien en tenofovirdisoproksielfumaraat: Kruisweerstandigheid onder sekere nukleosied trutranskriptase inhibeerders (NRTI's) is vasgestel. Die M184V/I en/of K65R substitusies wat *in vitro* deur die kombinasie van emtrisitabien en tenofovir geselekteer is, word ook gesien in sommige MIV-isolate van pasiënte in wie die behandeling met tenofovir in kombinasie met óf lamivudien, óf emtrisitabien, en óf abakavir óf didanosien misluk het. Kruisweerstandigheid tussen hierdie middels kan dus voorkom by 'n pasiënt wie se virus enige een of beide van hierdie aminosuur substitusies huisves.

Emtrisitabien: Emtrisitabien-weerstandbiedende isolate (M184V/I) het kruisweerstandigheid teen lamivudien en salsitabien getoon. Hierdie isolate van uitermate behandelingservare pasiënte wat die M184V/I aminosuur substitusie in die konteks van ander NRTI weerstandigheid-geassosieerde substitusies bevat, kan vatbaarheid vir tenofovir behou. MIV-1 isolate met die K65R substitusie, *in vivo* geselekteer deur abakavir, didanosien, tenofovir en salsitabien, het 'n afname in vatbaarheid vir inhibisie deur emtrisitabien getoon. Virusse wat mutasies bevat wat hulle minder vatbaar maak vir stavudien en sidovudien (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) of didanosien (L74V), bly sensitief vir emtrisitabien. MIV-1 virale isolate met die K103N substitusie wat met weerstandigheid teen NRTI's geassosieer word, was vatbaar vir emtrisitabien.

Tenofovirdisoproksielfumaraat: MIV-1 met multinukleosied weerstandigheid met 'n T69S dubbelinvoeging mutasie in trutranskriptase toon verminderde vatbaarheid vir tenofovir.

Antivirale aktiwiteit

Emtrisitabien en tenofovirdisoproksielfumaraat: In kombinasie studies wat die *in vitro* antivirale aktiwiteit van emtrisitabien en tenofovir saam geëvalueer het, is sinergistiese antivirale effekte waargeneem.

Emtrisitabien: Die *in vitro* antivirale aktiwiteit van emtrisitabien teen laboratorium- en kliniese isolate van MIV is in limfoblastoïede sellyne, die MAGI-CCR5 sellyn en perifere bloed mononukleêre selle geëvalueer. In geneesmiddel-kombinasie studies van emtrisitabien met nukleosied trutranskriptaseremmers (abakavir, lamivudien, stavudien, salsitabien, sidovudien), nie-nukleosied trutranskriptaseremmers (delavirdien, efavirens, nevirapien) en proteaseremmers (amprenavir, nelfinavir, ritonavir, sakinavir), is additiewe tot sinergistiese effekte waargeneem. Die meeste van hierdie geneesmiddel-kombinasies is nie by mense bestudeer nie. Emtrisitabien het *in vitro* antivirale aktiwiteit teen MIV-1 klades A, B, C, D, E, F en G vertoon en het stam-spesifieke aktiwiteit teen MIV-2.

Tenofovirdisoproksielfumaraat: Die *in vitro* antivirale aktiwiteit van tenofovir teen laboratorium- en kliniese isolate van MIV-1 is in limfoblastoïede sellyne, primêre monosiet-/makrofaag selle en perifere bloed limfosiete geëvalueer. In die middel kombinasie studies van tenofovir met die nukleosied trutranskriptaseremmers (abakavir, didanosien lamivudien, stavudien, salsitabien, sidovudien), nie-nukleosied trutranskriptaseremmers (delavirdien, efavirens, nevirapien) en proteaseremmers (amprenavir, nelfinavir, ritonavir, sakinavir), is additiewe tot sinergistiese effekte waargeneem. Tenofovir toon *in vitro* antivirale aktiwiteit teen MIV-1 klades A, B, C, D, E, F, G en O.

Farmakokinetiese eienskappe:

Farmakokinetika in volwassenes:

Emtrisitabien: Die farmakokinetiese eienskappe van emtrisitabien word in Tabel 1 opgesom.

Emtrisitabien: Na orale toediening van emtrisitabien (200 mg) word dit vinnig geabsorbeer; piek plasmakonsentrasies word binne omtrent 1 tot 2 uur na dosering bereik. Die *in vitro* binding van emtrisitabien aan menslike plasmaproteïene is < 4 % en is onafhanklik van die konsentrasie oor die reikwydte van 0,02 tot 200 µg/ml. Na toediening van radioaktief gemerkte emtrisitabien is ongeveer 86 % in die urien en 13 % as metaboliete herwin. Die metaboliete van emtrisitabien sluit 3'-sulfoksieddiastereomere en hulle glukoroonsuur konjugaat in. Emtrisitabien word deur middel van 'n kombinasie van aktiewe tubulêre sekresie en glomerulêre filtrasie geëlimineer. Na 'n enkele orale dosis van emtrisitabien (200 mg) is die halfleeftyd van emtrisitabien in die plasma ongeveer 10 uur.

Tenofovirdisoproksielfumaraat: Die farmakokinetiese eienskappe van tenofovirdisoproksielfumaraat word in Tabel 1 opgesom. Na die orale toediening van tenofovir word maksimum tenofovir serumkonsentrasies na 1,0 ± 0,4 uur bereik. Die *in vitro* binding van tenofovir aan menslike plasmaproteïene is < 0,7 % en is onafhanklik van die konsentrasie oor die reikwydte van 0,01 tot 25 µg/ml. Ongeveer 70 tot 80 % van die intraveneuse dosis van tenofovir word as onveranderde middel in die urien herwin. Tenofovir word deur middel van 'n kombinasie van aktiewe tubulêre sekresie en glomerulêre filtrasie geëlimineer. Na toediening van 'n enkele orale dosis van tenofovir, is die terminale eliminasiehalfleeftyd ongeveer 17 uur.

Tabel 1:

Enkeldosis farmakokinetiese parameters vir emtrisitabien en tenofovir by volwassenes[1]

	Emtrisitabien	Tenofovir
Vastende orale biobeskikbaarheid[2] (%)	92 (83,1 tot 106,4)	25 (NC tot 45,0)
Terminale eliminasiehalfleeftyd in plasma[2] (%)	10 (7,4 tot 18,0)	17 (12,0 tot 25,7)
K_{maks}[3] (µg/ml)	1,8 ± 0,72[4]	0,30 ± 0,09
AOK[3] (µg·hr/ml)	10,0 ± 3,12[4]	2,29 ± 0,69
CL/F[3] (ml/min)	302 ± 94	1043 ± 115
CL_{renaal}[3] (ml/min)	213 ± 89	243 ± 33

1. NC = Nie bereken nie.
2. Mediaan (reeks).
3. Gemiddeld (± SD).
4. Data word as waardes by ewewigstoestand aangegee.

Die effek van voedsel op orale absorpsie:

Die kombinasie tablet kan met of sonder voedsel gegee word. Toediening van die kombinasie tablet na 'n baie vetterige maaltyd (784 kkal; 49 g vet) of 'n ligte maaltyd (373 kkal; 8 g vet) het die tyd tot K_{maks} met ongeveer 0,75 uur vertraag. Die gemiddelde toenames in tenofovir se AOK en K_{maks} was onderskeidelik ongeveer 35 % en 15 %, wanneer dit saam met 'n baie vetterige of ligte maaltyd toegedien is, in vergelyking met toediening in 'n vastende toestand. In vorige ondersoeke na veiligheid en doeltreffendheid is tenofovir saam met voedsel toegedien. Daar was geen effek op die sistemiese blootstelling van emtrisitabien (AOK en K_{maks}) nadat die kombinasie tablet saam met 'n baie vetterige of 'n ligte maaltyd toegedien is nie.

Spesiale populasies:

Ras:

Emtrisitabien: Geen farmakokinetiese verskille vanweë ras is na toediening van emtrisitabien (200 mg) opgespoor nie.

Tenofovirdisoproksielfumaraat: Buiten Kaukasiërs, was daar te min ander rasse en etniese groepe ondersoek om die potensiële farmakokinetiese verskille tussen hierdie bevolkings na die toediening van tenofovirdisoproksielfumaraat voldoende te kan bepaal.

Pediatriese pasiënte:

Die farmakokinetika van emtrisitabien en tenofovir is nie ten volle by kinders (< 12 jaar met 'n gewig minder as 35 kg) evalueer nie (sien **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).

Geriatriese pasiënte:

Die farmakokinetika van emtrisitabien en tenofovir is nie ten volle by bejaardes (> 65 jaar) evalueer nie (sien **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).

Gebruik by pasiënte met ingekorte nierfunksie:

Die farmakokinetiese eienskappe van emtrisitabien en tenofovir is gewysig by pasiënte met ingekorte nierfunksie (sien **"KONTRA-INDIKASIES"**, **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**, **"Ingekorte nierfunksie"**). By pasiënte met kreatinienopruiming < 50 ml/min, is die K_{maks} en AOK_{∞} van beide emtrisitabien en tenofovir beduidend verhoog.

TYRICTEN 200/300 mg moet nie gebruik word by pasiënte met kreatinienopruiming < 50 ml/min of by pasiënte met eindstadium nierversaking wat dialise benodig nie (sien **"KONTRA-INDIKASIES"**, **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**, **"Ingekorte nierfunksie"**).

Moenie **TYRICTEN 200/300 mg** vir die pre-blootstelling profilakse (PrEP) indikasie by MIV-1 onbesmette individue met 'n kreatinienopruiming <60 ml/min gebruik nie (sien **"KONTRA-INDIKASIES"**, **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).

Pasiënte met ingekorte lewerfunksie:

Die farmakokinetiese eienskappe van tenofovir, na 'n enkeldosis van 300 mg tenofovirdisoproksielfumaraat, is ondersoek by pasiënte met matig tot erg ingekorte lewerfunksie wat nie met MIV geïnfekteer is nie. Daar was geen beduidende veranderinge in die farmakokinetika van tenofovir by pasiënte met ingekorte lewerfunksie in vergelyking met pasiënte met normale lewerfunksie nie. Die farmakokinetika van die kombinasie-tablet of emtrisitabien is nie by pasiënte met ingekorte lewerfunksie bestudeer nie. Emtrisitabien word egter nie beduidend deur lewerensieme gemetaboliseer nie, die effek van ingekorte lewerfunksie behoort dus beperk te wees.

INDIKASIES

TYRICTEN 200/300 mg is aangedui in kombinasie met ander antiretrovirale middels (soos proteaseremmers of nie-nukleosied trutranskriptaseremmers) vir die behandeling van MIV-1 infeksie by volwassenes.

TYRICTEN 200/300 mg word aangedui in kombinasie met veiliger seksuele praktyke vir pre-blootstelling profilakse (PrEP) by bevestigde MIV-1 onbesmette volwassenes, om die risiko van seksueel verworwe MIV-1 by volwassenes met 'n hoë risiko te verminder; met dien verstande dat maksimum nakoming van die behandeling gemoniteer kan word.

KONTRA-INDIKASIES

TYRICTEN 200/300 mg word teenaangedui by:

- Pasiënte met voorheen bewese hipersensitiwiteit vir enige van die komponente van **TYRICTEN 200/300 mg**.
- Kreatinienopruiming (KrO) < 60 ml/min indien gebruik vir MIV PrEP).
- Kreatinienopruiming (KrO) < 50 ml/min) indien gebruik vir die behandeling van MIV-1.
- Swangerskap en borsvoeding (sien **"MENSLIKE VOORTPLANTING"**).

TYRICTEN 200/300 mg moet nie gelyktydig met ander tenofovir-bevattende produkte, of met ander emtrisitabien-bevattende produkte gegee word nie. **TYRICTEN 200/300 mg** moet nie saam met lamivudien-bevattende produkte gegee word nie, vanweë die ooreenkomste tussen emtrisitabien en lamivudien.

TYRICTEN 200/300 mg moet nie gebruik word vir pre-blootstelling profilakse (PrEP) by individue wat met onbekende of positiewe MIV-1-status nie. **TYRICTEN 200/300 mg** moet nie gebruik word by individue wat nie met volle toewyding aan die behandeling sal voldoen nie.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS

Daar is geen studieresultate wat die effek van **TYRICTEN 200/300 mg** op die kliniese progressie van MIV-1 aandui nie.

Dit word nie aanbeveel dat **TYRICTEN 200/300 mg** as 'n komponent van 'n drievoudige nukleosied regimen gebruik word nie.

Individue moet gewaarsku word dat volle nakoming van behandeling noodsaaklik is vir doeltreffendheid in die voorkoming van MIV-1-oordrag en hulle moet ten volle ingelig word oor die gebruik van ander voorkomende maatreëls, waaronder versperring voorbehoedmiddels (kondome).

Individue wat nie ten volle toegewyd is, of wat nie vertrou kan word om aan die vereistes vir die behandeling te voldoen nie, moet nie **TYRICTEN 200/300 mg** vir profilakse van MIV-1-oordrag gebruik nie.

Melksuurasidose/Erge hepatomegalie met steatose:

Melksuurasidose en erge hepatomegalie met steatose, waaronder gevalle van sterftes, is met die gebruik van nukleosied analoë soos **TYRICTEN 200/300 mg**, alleen of in kombinasie met antiretrovirale middels, aangemeld. Die meeste van hierdie gevalle was by vrouens gewees. Vetsug en verlengde nukleosiedblootstelling kan risikofaktore wees. Uiterste omsigtigheid is nodig wanneer nukleosied analoë, soos **TYRICTEN 200/300 mg,** aan enige pasiënt met bekende risikofaktore vir lewersiekte toegedien word; tog is komplikasies ook by pasiënte met geen bekende risikofaktore nie aangemeld. Behandeling met **TYRICTEN 200/300 mg** moet gestaak word by enige pasiënt wie se kliniese of laboratorium bevindings aanduidend is van die ontwikkeling van melksuurasidose of duidelike hepatotoksisiteit (wat hepatomegalie met steatose, selfs in die afwesigheid van opvallende toenames in transaminases kan insluit).

Melksuurasidose/Hiperlaktatemie:

Gebruik van **TYRICTEN 200/300 mg** kan lei tot potensieel noodlottige melksuurasidose, vanweë mitochondriese disfunksie.

Kliniese kenmerke is nie-spesifiek en sluit in naarheid, braking, buikpyn, dispnee, moegheid en gewigsverlies. By pasiënte met verdagte simptome of biochemie moet die veneuse laktaatkonsentrasie (normaal < 2 mmol/ℓ) en serumbikarbonaat bepaal word, waarna dan soos volg opgetree word:

Laktaat 2 tot 5 mmol/ℓ met weinige simptome: skakel oor na medisynes wat minder geneig is om melksuurasidose te veroorsaak.

Laktaat 5 tot 10 mmol/l met simptome en/of met verminderde standaard bikarbonaat: STAAK **TYRICTEN 200/300 mg** en verander die behandelingsopsie. Sodra die laktaat gestabiliseer het, gebruik medisynes wat minder waarskynlik melksuurasidose behoort te veroorsaak. Sluit ander oorsake uit, (bv. sepsis, uremie, diabetiese ketoasidose, tirotoksikose en hipertireose).

Laktaat > 10 mmol/l - STAAK alle behandeling. (80 % mortaliteit).

Die bogenoemde laktaatwaardes kan moontlik nie van toepassing wees op pediatriese pasiënte nie.

Wees versigtig wanneer **TYRICTEN 200/300 mg** aan pasiënte met bekende risikofaktore vir lewersiekte toegedien word.

Behandeling met **TYRICTEN 200/300 mg** moet by enige pasiënt met kliniese of laboratorium bevindings wat dui op die ontwikkeling van melksuurasidose of hepatotoksisiteit, gestaak word.

Pankreatitis:

Pankreatitis is by sommige pasiënte wat **TYRICTEN 200/300 mg** ontvang, waargeneem.

Pankreatitis moet oorweeg word wanneer 'n pasiënt buikpyn, naarheid, braking of verhoogde biochemiese merkers ontwikkel. Staak die gebruik van **TYRICTEN 200/300 mg** totdat diagnose van pankreatitis uitgesluit kan word.

Lewersiekte:

Gebruik van **TYRICTEN 200/300 mg** kan lei tot hepatomegalie vanweë nie-alkoholiese vetterige lewersiekte (hepatiese steatose). Die veiligheid en doeltreffendheid van **TYRICTEN 200/300 mg** is nog nie by pasiënte met belangrike onderliggende lewerversteurings/siektes bepaal nie.

Pasiënte met voorafbestaande lewerdisfunksie, waaronder chroniese aktiewe hepatitis, het 'n verhoogde frekwensie van lewerfunksieversteurings tydens kombinasie antiretrovirale behandeling en moet gemoniteer word. As daar bewys is van verslegtende lewersiekte by sulke pasiënte, moet tydelike of permanente staking van behandeling oorweeg word.

In die geval van gelyktydige antivirale behandeling vir hepatitis B of C, raadpleeg asseblief ook die betrokke verpakkingsbiljette vir hierdie medisyne

Mitochondriese disfunksie:

Nukleosied en nukleotied analoë soos **TYRICTEN 200/300 mg** is *in vitro* en *in vivo* aangetoon om 'n wisselende mate van mitochondriese skade te berokken. Daar was verslae van mitochondriese disfunksie by MIV-negatiewe babas wat *in utero* en/of postnataal aan nukleosied analoë blootgestel was. Afgesien van melksuurasidose/hiperlaktatemie (sien hierbo), behels ander manifestasies van mitochondriese disfunksie hematologiese afwykings (anemie, neutropenie), en perifere neuropatie. Sommige neurologiese versteurings wat later begin het (hipertonie, stuiptrekkings, abnormale gedrag) is aangemeld. Dit is nie bekend of die neurologiese afwykings van verbygaande aard, of permanent is nie. Enige fetus wat *in utero* aan nukleosied en nukleotied analoë blootgestel word, selfs MIV-negatiewe babas/kinders, moet klinies en met laboratoriumtoetse opgevolg word en moet volledig ondersoek word vir moontlike mitochondriese disfunksie in geval van relevante tekens of simptome.

Pasiënte met MIV en hepatitis B of C virus ko-infeksie:

Alle pasiënte met MIV moet getoets word vir die teenwoordigheid van chroniese hepatitis B virus (HBV) voordat hulle met **TYRICTEN 200/300 mg** behandeling begin. Pasiënte met chroniese hepatitis B of C en wat met antiretrovirale middels behandel word, het 'n hoër risiko vir ernstige en potensieel noodlottige newe-effekte op die lewer.

Mediese praktisyns behoort die huidige MIV-behandelingsriglyne vir die optimale bestuur van MIV-infeksie by pasiënte wat terselfdertyd ook met hepatitis B virus (HBV) besmet is, te raadpleeg.

TYRICTEN 200/300 mg word nie vir die behandeling van chroniese HBV-infeksie aangedui nie en die veiligheid en doeltreffendheid van **TYRICTEN 200/300 mg** is nie by pasiënte wat beide met HBV en MIV besmet is, vasgestel nie.

In die geval van gelyktydige antivirale behandeling vir hepatitis B of C, raadpleeg asseblief die betrokke verpakkingsbiljette vir hierdie medisyne.

Pasiënte wat tegelykertyd met MIV en HBV besmet is en wat **TYRICTEN 200/300 mg** staak, moet noulettend opgevolg word met kliniese waarneming en laboratoriumtoetse na behandeling gestaak is. By pasiënte met gevorderde lewersiekte of sirrose word staking van behandeling nie aanbeveel nie, aangesien opflikkering van hepatitis na die behandeling tot hepatiese dekompensasie en lewerversaking kan lei.

Lewerfunksie moet noukeurig gemoniteer word, deur beide kliniese en laboratorium opvolging, vir ten minste verskeie maande by pasiënte wat **TYRICTEN 200/300 mg** gestaak het en wat met beide MIV en HBV geïnfekteer is. Indien toepaslik, kan die inleiding van behandeling vir hepatitis B geregverdig wees.

Ingekorte nierfunksie:

Emtrisitabien en tenofovir word hoofsaaklik deur die niere uitgeskei.

Ingekorte nierfunksie, insluitend gevalle van akute nierversaking en Fanconi se sindroom (renale tubulêre skade met erge hipofosfatemie) is in samewerking met die gebruik van tenofovir aangemeld (sien **"NEWE-EFFEKTE"** en **"KONTRA-INDIKASIES"**).

Dit word aanbeveel dat kreatinienopruiming by alle pasiënte bepaal word voordat behandeling begin word en soos wat klinies toepaslik is tydens behandeling met **TYRICTEN 200/300 mg**. Roetine monitering van die kreatinienopruiming en serumfosfor moet uitgevoer word by pasiënte wat 'n risiko het vir verswakte nierfunksie (sien **"KONTRA-INDIKASIES"**.)

Die gebruik van **TYRICTEN 200/300 mg** moet vermy word met gelyktydige of onlangse gebruik van 'n nefrotoksiese middel.

TYRICTEN 200/300 mg moet nie toegedien word aan pasiënte met kreatinienopruiming minder as 50 ml/min of aan pasiënte wat hemodialise benodig nie en ook nie vir pre-blootstelling profilakse by pasiënte met kreatinienopruiming minder as 60 ml/min nie (sien **"KONTRA-INDIKASIES"**).

Indien 'n afname in kreatinienopruiming by nie-geïnfekteerde individue ontwikkel tydens gebruik van **TYRICTEN 200/300 mg** vir PrEP, moet **TYRICTEN 200/300 mg** gestaak word (sien **"KONTRA-INDIKASIES"**).

Pasiënte met matige tot erge ingekorte nierfunksie:

By pasiënte met matige tot ernstige verswakte nierfunksie is die terminale halfleeftyd van **TYRICTEN 200/300 mg** langer, as gevolg van verminderde opruiming. **TYRICTEN 200/300 mg** moet dus nie by hierdie pasiënte gebruik word nie (sien **"KONTRA-INDIKASIES"**).

Waarskuwings en spesiale voorsorgmaatreëls betreffende interaksies:

TYRICTEN 200/300 mg moet nie saam met bykomende emtrisitabien of tenofovir toegedien word nie (sien **"KONTRA-INDIKASIES"**).

Lamivudien:

Vanweë die ooreenkomste tussen emtrisitabien en lamivudien moet **TYRICTEN 200/300 mg** nie gelyktydig saam met ander medisyne wat lamivudien, insluitend lamivudien en sidovudien ko-formulerings, lamivudien vir MIV, lamivudien vir HBV, abakavirsulfaat en lamivudien ko-formulering of abakavirsulfaat, lamivudien en sidovudien ko-formulerings toegedien word nie (sien **"KONTRA-INDIKASIES"**).

Didanosien:

Die gelyktydige dosering van tenofovirdisoproksielfumaraat en didanosien as gebufferde tablette, of enteries-bedekte kapsules, verhoog die K_{maks} en AOK van didanosien aansienlik. Die meganisme van die interaksie is onbekend. Hoër konsentrasies van didanosien kan didanosien-verwante newe-effekte, waaronder pankreatitis en neuropatie, potensieer.

By volwassenes wat > 60 kg weeg, moet die dosis van didanosien tot 250 mg verminder word as dit saam met **TYRICTEN 200/300 mg** toegedien word. Daar is geen inligting beskikbaar om 'n aanbeveling te kan maak oor aanpassing van die dosis van didanosien by pasiënte wat < 60 kg weeg nie. Wanneer dit gelyktydig toegedien word, kan **TYRICTEN 200/300 mg** en didanosien onder vastende toestande, of met 'n ligte ete (< 400 kkal, 20 % vet) geneem word.

Gelyktydige toediening van didanosien gebufferde tablet formulering met **TYRICTEN 200/300 mg** moet onder vastende toestande geskied (sien **"INTERAKSIES"**). Gelyktydige toediening van **TYRICTEN 200/300 mg** en didanosien moet met omsigtigheid geskied en pasiënte wat hierdie kombinasie ontvang moet noukeurig vir didanosien-geassosieerde newe-effekte gemoniteer word. Didanosien moet gestaak word by pasiënte wat didanosien-geassosieerde newe-effekte ontwikkel (sien **"NEWE-EFFEKTE"**).

Atasanavir en lopinavir/ritonavir:

Daar is aangetoon dat hierdie kombinasie 'n toename in die konsentrasie van tenofovir veroorsaak. Die meganisme van die interaksie is onbekend.

Pasiënte wat atasanavir en lopinavir/ritonavir en **TYRICTEN 200/300 mg** ontvang, moet vir **TYRICTEN 200/300 mg** -geassosieerde newe-effekte gemoniteer word en **TYRICTEN 200/300 mg** moet gestaak word by pasiënte wat **TYRICTEN 200/300 mg** -geassosieerde newe-effekte ontwikkel (sien **"NEWE-EFFEKTE"**).

Tenofovir verminder die AOK en K_{min} van atasanavir (sien **"INTERAKSIES"**).

Wanneer dit saam met **TYRICTEN 200/300 mg** toegedien word, word dit aanbeveel dat atasanavir 300 mg saam met ritonavir 100 mg gegee word.

Atasanavir sonder ritonavir moet nie saam met **TYRICTEN 200/300 mg** toegedien word nie.

Medisyne wat deur die niere uitgeskei word:

Emtrisitabien en tenofovirdisoproksielfumaraat:

Aangesien emtrisitabien en tenofovir hoofsaaklik deur die niere verwyder word, kan gelyktydige toediening van **TYRICTEN 200/300 mg** met medisyne wat die nierfunksie verminder of wat kompeteer vir aktiewe tubulêre sekresie, die serumkonsentrasies van emtrisitabien, tenofovir en/of ander stowwe wat deur die niere uitgeskakel word, verhoog (sien **"INTERAKSIES"**). 'n Paar voorbeelde sluit in, maar is nie beperk tot adefovir dipivoksiel, sidofovir, asiklovir, valasiklovir, gansiklovir en valgansiklovir nie.

Takrolimus kan die nierfunksie aantas. Deeglike monitering word dus aanbeveel wanneer dit saam met **TYRICTEN 200/300 mg** toegedien word (sien **"INTERAKSIES"**).

Effekte op die been:

Beenmineraaldigtheid:

Tenofovirdisoproksielfumaraat:

Tenofovir kombinasieterapie word geassosieer met verminderde beenmineraaldigtheid.

Tydens behandeling met **TYRICTEN 200/300 mg** moet bepalings van beendigtheid (BMD) oorweeg word vir pasiënte wat 'n geskiedenis van patologiese beenbreuke het, of wat ander risikofaktore vir osteoporose, of beenverlies het. Die effek van die aanvulling met kalsium en vitamien D is nie ondersoek nie. Indien beenafwykings vermoed word, moet geskikte konsultasie verkry word. Monitering van beenmineraaldigtheid moet in ag geneem word vir MIV-besmette pasiënte met 'n geskiedenis van patologiese beenfrakture, of wat 'n risiko vir osteopenie het.

By kliniese studies op MIV-1 nie-geïnfekteerde individue is dalings in BMD ook waargeneem. In 'n pre-blootstelling studie op mans wat met mans seks gehad het (MSM), het 'n sub-studie van 503 proefpersone gemiddelde veranderinge in BMD t.o.v. die basislyn, wat gewissel het van -0,4 % tot -1,0 % oor die totale heup, rug, femorale nek en trogantergebied in die emtrisitabien/tenofovirdisoproksiel kombinasiegroep gevind, in vergelyking met die plasebogroep. Beenbreuke is by 1,7 % van die emtrisitabien/tenofovirdisoproksiel kombinasiegroep in vergelyking met 1,4 % in die plasebogroep aangemeld. Geen korrelasie tussen BMD en frakture is opgemerk nie. In 'n pre-blootstelling studie in heteroseksuele paartjies waar een van die vennote MIV-1 besmet was, is 'n soortgelyke koers van frakture gevind in die groepe wat behandeling ontvang het as by die plasebogroepe (0,8 % en 0,6 % onderskeidelik). Geen BMD ondersoeke is in hierdie studie gedoen nie. Gevalle van osteomalasie (wat verband hou met proksimale renale tubulopatie) is in assosiasie met die gebruik van tenofovir DF, soos bevat in **TYRICTEN 200/300 mg**, aangemeld (sien **"NEWE-EFFEKTE"**).

Osteonekrose:

Alhoewel die etiologie as multifaktoriaal beskou word (waaronder gebruik van kortikosteroïede, alkohol, erge immuunonderdrukking, hoër liggaamsmassa-indeks), is gevalle van osteonekrose aangemeld, veral by pasiënte met gevorderde MIV-siekte en/of langtermyn blootstelling aan kombinasie Anti-Retrovirale Terapie (cART). Pasiënte moet aangeraai word om mediese raad in te win as hulle pyne in die gewrigte, gewrigstyfheid of probleme met beweging ervaar.

Lipodistrofie en metaboliese afwykings:

TYRICTEN 200/300 mg is geassosieer met die herverspreiding/akkumulasie van liggaamsvet, waaronder sentrale obesiteit, dorso-servikale vetvergroting (buffelskof), perifere wegkwyning, wegkwyning van die gesig, borsvergroting en verhoogde serum-lipiede en glukosekonsentrasies by MIV pasiënte, en 'n "cushingagtige voorkoms" is by pasiënte wat antiretrovirale behandeling, soos **TYRICTEN 200/300 mg** ontvang, waargeneem.

Die meganisme en langtermyn gevolge van hierdie voorvalle is tans onbekend. 'n Oorsaaklike verwantskap is nie bepaal nie.

Kliniese ondersoek moet evaluering van fisiese tekens vir herverspreiding van vet insluit. Pasiënte met tekens van lipodistrofie moet 'n deeglike kardiovaskulêre risikobepaling ondergaan.

Immuunrestourasie inflammatoriese sindroom:

Immuunrestourasie inflammatoriese sindroom (IRIS) is 'n immunopatologiese reaksie, wat volg op die vinnige herstel van patogeen-spesifieke immuniteitsreaksies op voorafbestaande antigene, gekombineer met immuunsiedregulasie, wat kort na aanvang van kombinasie- Anti-Retrovirale Terapie (cART) voorkom. So 'n reaksie presenteer deur paradoksale agteruitgang van opportunistiese infeksies wat behandel word, of met ontmaskering van 'n asimptomatiese opportunistiese siekte, dikwels met 'n atipiese inflammatoriese aanbieding. IRIS ontwikkel gewoonlik binne die eerste drie maande van aanvang van ART en kom meer algemeen voor by pasiënte met lae CD4-tellings. Algemene voorbeelde van IRIS-reaksies op opportunistiese siektes is pulmonale tuberkulose, sitomegalovirus retinitis, *Pneumocystis jirovecii* pneumonie (PCP), kriptokokmeningitis en ander vorme van tuberkulose en atipiese mikobakteriële infeksies.

Geskikte behandeling van die opportunistiese siekte moet ingestel of voortgesit word en ART moet volgehou word. Inflammatoriese verskynsels klaar gewoonlik na 'n paar weke op. Erge gevalle kan op glukokortikoïede reageer, maar daar is slegs beperkte bewys daarvoor by pasiënte met tuberkulese IRIS. Outo-immuunversteurings (soos Graves se siekte) is ook as IRIS-reaksies aangemeld; die aangemelde aanvangstyd is egter meer veranderlik en hierdie gebeure kan baie maande na aanvang van behandeling voorkom.

Immuunrestourasie inflammatoriese sindroom is aangemeld by pasiënte wat kombinasie antiretrovirale terapie, waaronder **TYRICTEN 200/ 300 mg**, ontvang het. Tydens die eerste fase van behandeling met **TYRICTEN 200/300 mg** kan pasiënte wie se immuunstelsel 'n reaksie toon, 'n inflammatoriese reaksie op pynlose of residuele opportunistiese infeksies, wat verdere evaluering en behandeling kan benodig, ontwikkel.

Opportunistiese infeksies:

Pasiënte wat **TYRICTEN 200/300 mg** ontvang, moet ingelig word dat hulle steeds opportunistiese infeksies en ander komplikasies van MIV-infeksie kan opdoen en dat hulle noukeurige toesig van 'n gesondheidsorgkundige, wat ervare is met die behandeling van pasiënte met geassosieerde MIV-siekte, moet ontvang. Gereelde monitering van virusladings en CD4-tellings moet gedoen word.

Die risiko van MIV oordrag aan ander mense:

Pasiënte moet ingelig word dat huidige antiretrovirale terapie, waaronder **TYRICTEN 200/300 mg**, nie die risiko van oordrag van MIV aan ander mense deur seksuele kontak of deur bloedkontaminasie verhoed nie. Geskikte voorsorgmaatreëls moet voortdurend toegepas word.

Omvattende bestuur om die risiko om MIV-1 op te doen, te verminder:

Gebruik **TYRICTEN 200/300 mg** vir pre-blootstelling profilakse slegs as deel van 'n omvattende voorkomingstrategie, wat ander voorkomingsmaatreëls, soos veiliger sekspraktyke insluit, want **TYRICTEN 200/300 mg** is nie altyd doeltreffend om te voorkom dat MIV-1 opgedoen word nie.

- Adviseer nie-geïnfekteerde individue oor veiliger sekspraktyke, wat insluit die konsekwente en korrekte gebruik van kondome, kennis van hul MIV-1-status en dié van hul maat(s), en gereelde toetsing vir ander seksueel-oordraagbare infeksies wat MIV-1-oordrag kan fasiliteer (soos sifilis en gonorree).
- Lig nie-geïnfekteerde individue hieroor in en ondersteun hulle pogings om riskante seksuele gedrag te verminder.

Gebruik TYRICTEN 200/300 mg slegs by individue wat bevestig is om MIV-negatief te wees, om die risiko vir die verkryging van MIV-1 te verminder. MIV-1 weerstandige substitusies kan na vore kom by individue met ongediagnoseerde MIV-1 infeksie, wat slegs TYRICTEN 200/300 mg neem, want TYRICTEN 200/300 mg alleen behels nie 'n volledige behandelingsregimen vir MIV-1 nie. Daarom moet sorg gedra word om TYRICTEN 200/300 mg blootstelling by MIV-besmette individue te vermy (sien "KONTRA-INDIKASIES").

- **Heelwat MIV-1-toetse, soos sneltoetse, spoor anti-MIV-teenliggaampies op en kan nie MIV-1 tydens die akute stadium van infeksie bepaal nie. Voor aanvang van TYRICTEN 200/300 mg vir 'n PrEP-indikasie, evalueer seronegatiewe individue vir huidige of onlangse tekens of simptome konsistent met akute virale infeksies (bv. koors, moegheid, mialgie, veluitslag, ens.) en vra oor moontlike voorvalle van blootstelling (bv. onbeskermde seks, of 'n kondoom wat kon skeur tydens seks met 'n MIV-1 besmette vennoot), wat in die afgelope maand kon plaasgevind het.**
- **Indien kliniese simptome konsistent met akute virale infeksie teenwoordig is en daar was vermoedelik onlangs (<1 maand) blootstelling, vertraag die aanvang van PrEP vir minstens een maand en herbevestig MIV-1-status, of gebruik 'n goedgekeurde toets as 'n hulpmiddel by die diagnose van MIV-1 infeksie, insluitend akute of primêre MIV-1 infeksie.**
- **Terwyl TYRICTEN 200/300 mg vir 'n PrEP-indikasie gebruik word, moet MIV-1 siftingstoetse ten minste een keer elke 3 maande herhaal word. Indien simptome konsistent met akute MIV-1 besmetting na 'n voorval van potensiële blootstelling ontwikkel, moet PrEP gestaak word totdat 'n negatiewe infeksiestatus met behulp van 'n goedgekeurde toets as hulpmiddel by die diagnose van MIV-1, insluitend akute of primêre MIV-1 infeksie, bevestig word.**

Adviseer nie-geïnfekteerde individue om streng te hou by die aanbevole **TYRICTEN 200/300 mg** doseringskedule.

Die doeltreffendheid van **TYRICTEN 200/300 mg** in die vermindering van die risiko vir die verkryging van MIV-1 word sterk gekorreleer met meewerkendheid, soos aangetoon m.b.v. meetbare vlakke van die medisyne in kliniese toetse.

Vroeë virologiese mislukking:

Kliniese studies by MIV-1 besmette pasiënte het getoon dat sekere regimens wat slegs drie nukleosied trutranskriptaseremmers (NRTIs) bevat, oor die algemeen minder doeltreffend is as regimens wat twee NRTIs in kombinasie met óf 'n nie-nukleosied-trutranskriptaseremmer, of 'n MIV-1 proteaseremmer, bevat. In die besonder was vroeë virologiese mislukking en 'n hoë koers van weerstandige substitusies aangemeld.

Drievoudige nukleosied regimens moet dus met versigtigheid gebruik word. Pasiënte op 'n behandeling wat slegs 'n drievoudige nukleosied regimen gebruik, moet noukeurig gemoniteer en oorweeg word vir modifikasie van die behandeling.

Pediatriese gebruik:

Die veiligheid en doeltreffendheid by pediatriese pasiënte is nie bepaal nie.

Geriatriese gebruik :

Oor die algemeen moet die dosis vir ouer pasiënte versigtig gekies word, met inagneming van die hoër frekwensie van verminderde lewer-, nier-, of hartfunksie en van gepaardgaande siekte of behandeling met ander medisyne.

Effek op die vermoë om te bestuur en masjinerie te gebruik:

Geen studies is uitgevoer oor die effek van tenofovirdisoproksielfumaraat of emtrisitabien op die vermoë om te bestuur of masjinerie te hanteer nie. Duiseligheid is egter aangemeld tydens behandeling met beide tenofovirdisoproksielfumaraat en emtrisitabien. Pasiënte moet nie bestuur en masjinerie gebruik voordat hulle nie bepaal het hoe hulle aangetas word nie.

Laktose waarskuwing:

TYRICTEN 200/300 mg bevat laktose.

Pasiënte met die seldsame oorerflike kondisies van galaktose intoleransie bv. galaktosemie, Lapp-laktase tekort, glukose-galaktose wanabsorpsie of fruktose intoleransie moet nie **TYRICTEN 200/300 mg** gebruik nie.

Laktose kan 'n effek hê op die glukemiese beheer van pasiënte met diabetes mellitus.

INTERAKSIES

TYRICTEN 200/300 mg:

Geen interaksiestudies is met **TYRICTEN 200/300 mg** uitgevoer nie.

Die stabiele staat farmakokinetika van emtrisitabien en tenofovir was onveranderd nadat emtrisitabien en tenofovirdisoproksielfumaraat in kombinasie, versus elke middel alleen, toegedien is.

In vitro en kliniese farmakokinetiese geneesmiddel-interaksiestudies het getoon dat die potensiaal vir CYP450-gemedieerde interaksies, waar emtrisitabien en tenofovir met ander medisinale produkte betrokke was, laag is.

Emtrisitabien en tenofovir word hoofsaaklik deur die niere uitgeskei, deur 'n kombinasie van glomerulêre filtrasie en aktiewe tubulêre sekresie. Geen geneesmiddelinteraksies weens kompetisie vir renale uitskeiding is waargeneem nie. Die gesamentlike toediening van **TYRICTEN 200/300 mg** saam met medisynes wat deur aktiewe tubulêre sekresie geëlimineer word, kan egter die konsentrasies van emtrisitabien, tenofovir en/of die gesamentlik toegediende middels verhoog.

Medisyne wat nierfunksie verminder kan konsentrasies van emtrisitabien en/of tenofovir verhoog. Geen klinies betekenisvolle geneesmiddelinteraksies is tussen emtrisitabien en famsiklovir, indinavir, stavudien en tenofovirdisoproksielfumaraat waargeneem nie (sien Tabelle 2 en 3). Insgelyks is geen klinies belangrike interaksies tussen tenofovirdisoproksielfumaraat en abakavir, adefovirdipivoksiel, ribavirien, efavirens, emtrisitabien, indinavir, lamivudien, lopinavir/ritonavir, metadoon, nelfinavir, orale voorbehoedmiddels, en sakinavir/ritonavir in studies wat by gesonde vrywilligers uitgevoer is, waargeneem nie (sien Tabelle 4 en 5).

Tabel 2:

Geneesmiddelinteraksies: Veranderinge in farmakokinetiese parameters vir emtrisitabien in die teenwoordigheid van die gesamentlik toegediende medisyne [1]

Gesamentlik toegediende medisyne	Dosis van gesamentlik toegediende medisyne (mg)	Emtrisitabien dosis (mg)	N	% Verandering van emtrisitabien farmakokinetiese parameters[2] (90 % VI)		
				K_{maks}	AOK	K_{min}
Tenofovir DF	300 een keer daagliks x 7 dae	200 een keer daagliks x 7 dae	17	⇔	⇔	↑ 20 (↑ 12 tot ↑ 29)
Sidovudien	300 twee keer daagliks x 7 dae	200 een keer daagliks x 7 dae	27	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	n.v.t.
Famsiklovir	500 x 1	200 x 1	12	⇔	⇔	n.v.t.
Stavudien	40 x 1	200 x 1	6	⇔	⇔	n.v.t.

1. Alle interaksiestudies is by gesonde vrywilligers uitgevoer.
2. ↑ = Toename; ↓ = Afname; ⇔ = Geen effek; n.v.t. = Nie van toepassing nie.

Tabel 3:

Geneesmiddelinteraksies: Verandering in farmakokinetiese parameters vir die gesamentlik toegediende medisyne in die teenwoordigheid van emtrisitabien[1]

Gelyktydig toegediende medisyne	Dosis van gelyktydig toegediende medisyne (mg)	Emtrisitabien dosis (mg)	N	% Verandering van emtrisitabien farmakokinetiese parameters[2] (90 % VI)		
				K_{maks}	AOK	K_{min}
Tenofovir DF	300 een keer daagliks x 7 dae	200 een keer daagliks x 7 dae	17	⇔	⇔	⇔
Sidovudien	300 twee keer daagliks x 7 dae	200 een keer daagliks x 7 dae	27	↑ 17 (↑ 0 tot ↑ 38)	↑ 13 (↑ 5 tot ↑ 20)	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	n.v.t.
Famsiklovir	500 x 1	200 x 1	12	⇔	⇔	n.v.t.
Stavudien	40 x 1	200 x 1	6	⇔	⇔	n.v.t.

1. Alle interaksiestudies is by gesonde vrywilligers uitgevoer.
2. Toename = ↑; Afname = ↓ ; Geen effek = ⇔ ; n.v.t. = Nie van toepassing nie.

Tabel 4:

Geneesmiddelinteraksies: Verandering in farmakokinetiese parameters vir tenofovir[1] **in die teenwoordigheid van die gesamentlik toegediende medisyne.**

Gesamentlik toegediende medisyne	Dosis van gesamentlik toegediende medisyne (mg)	N	% Verandering van tenofovir farmakokinetiese Parameters[2] (90 % VI)		
			K_{maks}	AOK	K_{min}
Abakavir	300 een keer	8	⇔	⇔	NC
Adefovir dipivoksiel	10 een keer	22	⇔	⇔	NC
Atasanavir	400 een keer daagliks x 14 dae	33	↑ 14 (↑ 8 tot ↑ 20)	↑ 24 (↑ 21 tot ↑ 28)	↑ 22 (↑ 15 tot ↑ 30)
Didanosien (enteries-bedek)	400 een keer	25	⇔	⇔	⇔
Didanosien (gebuffer)	250 of 400 een keer daagliks x 7 dae	14	⇔	⇔	⇔
Efavirens	600 een keer daagliks x 14 dae	29	⇔	⇔	⇔
Emtrisitabien	200 een keer daagliks x 7 dae	17	⇔	⇔	⇔
Indinavir	800 drie keer daagliks x 7 dae	13	↑ 14 (↓ 3 tot ↑ 33)	⇔	⇔
Lamivudien	150 twee keer daagliks x 7 dae	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twee keer daagliks x 14 dae	24	⇔	↑ 32 (↑ 25 tot ↑ 38)	↑ 51 (↑ 37 tot ↑ 66)
Nelfinavir	1 250 twee keer daagliks x 14 dae	29	⇔	⇔	⇔
Sakinavir/ Ritonavir	1 000/100 twee keer daagliks x 14 dae	35	⇔	⇔	↑ 23 (↑ 16 tot ↑ 30)

1. Pasiënte ontvang tenofovir DF 300 mg een keer daagliks.
2. Toename = ↑; Afname = ↓; Geen effek = ⇔; NC = Nie bereken nie.
3. Reyataz S.A. voorskrifinligting (Bristol-Myers Squibb).

Tabel 5:

Geneesmiddelinteraksies: Verandering in farmakokinetiese parameters vir die gesamentlik toegediende medisyne in die teenwoordigheid van tenofovir.

Gesamentlik toegediende medisyne	Dosis van gesamentlik toegediende medisyne (mg)	N	% Verandering van gesamentlik toegediende medisyne se farmakokinetiese parameters[1] (90 % VI)		
			K_{maks}	AOK	K_{min}
Abakavir	300 een keer	8	↑ 12 (↓ 1 tot 26)	⇔	n.v.t.
Adefovir-dipivoksiel	10 een keer	22	⇔	⇔	n.v.t.
Atasanavir [2]	400 een keer daagliks x 14 dae	34	↓ 21 (↓ 27 tot ↓ 14)	↓ 25 (↓ 30 tot ↓ 19)	↓ 40 (↓ 48 tot ↓ 32)
Atasanavir	Atasanavir: Ritonavir 300/100 een keer daagliks x 42 dae	10	↓ 28 (↓ 50 tot ↑ 5)	↓ 25[3] (↓ 42 tot ↓ 3)	↓ 23[3] (↓ 46 tot ↑ 10)
Efavirens	600 een keer daagliks x 14 dae	30	⇔	⇔	⇔
Emtrisitabien	200 een keer daagliks x 7 dae	17	⇔	⇔	↑ 20 (↑ 12 tot ↑ 29)
Indinavir	800 drie keer daagliks x 7 dae	12	↓ 11 (↓ 30 tot ↑ 12)	⇔	⇔
Lamivudien	150 twee keer daagliks x 7 dae	15	↓ 24 (↓ 34 tot ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/ Ritonavir 400/100 twee keer daagliks x 14 dae	24	⇔	⇔	⇔
Metadoon [4]	40 tot 110 een keer daagliks x 14 dae[5]	13	⇔	⇔	⇔
Nelfinavir M8- metaboliet	1 250 twee keer daagliks x 14 dae	29	⇔ ⇔	⇔ ⇔	⇔ ⇔

1. Toename =↑; Afname = ↓; Geen effek = ⇔ ; n.v.t. = Nie van toepassing nie.
2. REYATAZ S.A. voorskrifinligting (Bristol-Myers Squibb).
3. By MIV-geïnfekteerde pasiënte het die toevoeging van tenofovir DF tot atasanavir 300 mg plus ritonavir 100 mg tot AOK en K_{min} waardes van atasanavir gelei wat 2, 3 en 4- keer hoër was as die onderskeie waardes wat vir atasanavir 400 mg waargeneem is wanneer dit alleen gegee is.
4. R- (aktiewe), S- en totale metadoon blootstelling het ooreengestem, of dit nou alleen, of saam met tenofovir DF, gedoseer was.
5. Individuele proefpersone was op hulle gestabiliseerde dosis van metadoon onderhou. Daar was geen farmakodinamiese veranderings (opiaat-toksisiteit of onttrekkingsimptome of tekens) aangemeld nie.
6. Etinielestradiol 0,035 mg en 17-deasetielnorgestimaat 0,25 mg (farmakologies aktiewe metaboliet) se blootstelling was dieselfde, hetsy dit alleen of saam met tenofovir DF gedoseer was.
7. Toenames in die AOK en K_{min} sal na verwagting nie klinies relevant wees nie; gevolglik sal geen aanpassings in die dosis nodig wees as tenofovir DF en ritonavir-versterkte sakinavir saam toegedien word nie.

Na verskeie doserings aan MIV-negatiewe proefpersone wat chroniese instandhoudingsterapie met metadoon, óf orale voorbehoedmiddels, óf 'n enkele dosis van ribavirien ontvang, het die farmakokinetika van tenofovir by ewewigstoestand ooreengekom met dié wat in vorige studies waargeneem is, wat dui op 'n gebrek aan klinies belangrike interaksies tussen hierdie medisyne en die tenofovirdisoproksielfumaraat.

Kombinasies wat enige van die volgende medisynes bevat, afhangende van die hoeveelheid teenwoordig, kan ook 'n interaksie met **TYRICTEN 200/300 mg** hê. Die geneesmiddelinteraksies wat hier toegelig word, is gebaseer op studies wat met die individuele middels uitgevoer is.

Abakavir:

Gelyktydige toediening van abakavir en tenofovir het gelei tot 'n toename in die K_{maks} van abakavir.

Atasanavir en/of lopinavir/ritonavir:

Gelyktydige gebruik van atasanavir en **TYRICTEN 200/300 mg** kan lei tot hoër konsentrasies van tenofovir en afnames in die AOK en K_{min} van atasanavir. Dit word aanbeveel dat atasanavir saam met ritonavir toegedien word. Atasanavir moet nie sonder ritonavir saam met **TYRICTEN 200/300 mg** toegedien word nie.

Dit is aangetoon dat atasanavir en lopinavir/ritonavir die tenofovirkonsentrasies verhoog het. Die meganisme van die interaksie is onbekend. Moniteer pasiënte vir emtrisitabien/tenofovir-geassosieerde newe-effekte en staak **TYRICTEN 200/300 mg** by pasiënte wat hierdie newe-effekte ontwikkel.

Didanosien:

Die gesamentlike toediening van tenofovirdisoproksielfumaraat en didanosien lei tot veranderinge in die farmakokinetika van didanosien wat van kliniese betekenis kan wees. Tabel 6 is 'n opsomming van die effekte van tenofovirdisoproksielfumaraat op die farmakokinetika van didanosien. Die gelyktydige dosering van tenofovirdisoproksielfumaraat en didanosien gebufferde tablette of enteries-bedekte kapsules verhoog die K_{maks} en AOK van didanosien aansienlik.

Nadat didanosien 250 mg enteries-bedekte kapsules saam met tenofovirdisoproksielfumaraat toegedien was, was die sistemiese blootstellings van didanosien soortgelyk aan dié wat met slegs die 400 mg enteries-bedekte kapsules onder vastende kondisies waargeneem is. Die meganisme van die interaksie is onbekend.

Tabel 6:

Geneesmiddelinteraksies: Farmakokinetiese parameters vir didanosien in die teenwoordigheid van tenofovir.

Didanosien[1] dosis (mg)/ Metode van toediening[2]	Tenofovir metode van toediening[2]	N	% Verskil (90 % VI) vs. didanosien 400 mg alleen, vastend[3]	
			K_{maks}	AOK
Gebufferde tablette				
400 een keer daagliks 4 x 7 dae	Vastend vir 1 uur na didanosien	14	↑ 28 (↑ 11 tot ↑ 48)	↑ 44 (↑ 31 tot ↑ 59)
Enteries-bedekte kapsules				
400 een keer, vastend	Met voedsel, 2 h na didanosien	26	↑ 48 (↑ 25 tot ↑ 76)	↑ 48 (↑ 31 tot ↑ 67)
400 een keer, met voedsel	Gelyktydig met didanosien	26	↑ 64 (↑ 41 tot ↑ 89)	↑ 60 (↑ 44 tot ↑ 79)
250 een keer, vastend	Met voedsel, 2 h na didanosien	28	↓ 10 (↓ 22 tot ↑ 3)	⇔
250 een keer, vastend	Gelyktydig met didanosien	28	⇔	↑ 14 (0 tot ↑ 31)
250 een keer, met voedsel	Gelyktydig met didanosien	28	↓ 29 (↓ 39 tot ↓ 18)	↓ 11 (↓ 23 tot ↑ 2)

1. Sien **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"** betreffende die gebruik van didanosien met tenofovir.
2. Toediening met voedsel was met 'n ligte maaltyd (~ 373 kkal, 20 % vet).
3. Toename = ↑; Afname = ↓; Geen verskil = ⇔.
4. Dit sluit in 4 proefpersone wat < 60 kg weeg, wat ddl 250 mg ontvang het.

Emtrisitabien en tenofovirdisoproksielfumaraat:

TYRICTEN 200/300 mg kombinasie is 'n vastedosis produk. Addisionele emtrisitabien of tenofovirdisoproksielfumaraat moet nie saam met die kombinasie produk gebruik word nie.

Indinavir:

Die gelyktydige toediening van indinavir en tenofovir het tot 'n toename in tenofovir K_{maks} en 'n afname in indinavir K_{maks} gelei.

Lamivudien of produkte wat lamivudien bevat:

Weens ooreenkomste tussen emtrisitabien en lamivudien moet hierdie twee middels nie saam toegedien word nie; boonop word lamivudien se K_{maks} verminder met gelyktydige toediening van tenofovir.

MENSLIKE VOORTPLANTING

Swangerskap:

Die veiligheid van **TYRICTEN 200/300 mg** tydens swangerskap en borsvoeding is nie bepaal nie.

Daar is nie voldoende of goed gekontroleerde navorsingstudies by swanger vrouens nie. **TYRICTEN 200/300** moet nie by swangerskap gebruik word nie (sien **"KONTRA-INDIKASIES"**).

'n Betroubare metode van voorbehoeding moet gebruik word om swangerskap te vermy terwyl **TYRICTEN 200/300 mg** geneem word.

Borsvoeding:

Moeders wat met MIV geïnfekteer is, moet nie hulle babas borsvoed nie, om oordrag van MIV na die geboorte te voorkom.

Studies by rotte het aangedui dat tenofovir in melk uitgeskei word. Dit is nie bekend of tenofovir in mensmelk uitgeskei word nie. Dit is nie bekend of emtrisitabien in mensmelk uitgeskei word nie.

Vanweë die moontlikheid van MIV- oordrag en die moontlikheid van ernstige newe-effekte by babas wat borsvoeding kry, moet moeders wat TYRICTEN 200/300 mg ontvang, ingelig word om nie hulle babas te borsvoed nie.

DOSERING EN GEBRUIKSAANWYSINGS

Dosering by volwassenes vir die behandeling van MIV-1 infeksie:

Die dosis van **TYRICTEN 200/300 mg** is een tablet (wat 200 mg emtrisitabien en 300 mg tenofovirdisoproksielfumaraat bevat) een keer daagliks, mondeliks geneem, met of sonder kos.

Dosering vir Pre-Blootstelling Profilakse:

Die dosis van **TYRICTEN 200/300 mg** by volwassenes wat nie met MIV-1 geïnfekteer is nie, is een tablet (wat 200 mg emtrisitabien en 300 mg tenofovirdisoproksielfumaraat bevat) een keer daagliks, mondeliks geneem, met of sonder kos.

'n Aansienlike toename in blootstelling aan die medisyne het voorgekom nadat **TYRICTEN 200/300 mg** aan pasiënte met matig tot erg verswakte nierfunksie toegedien is (sien **"KONTRA-INDIKASIES"**).

Roetine monitering van die berekende kreatinienopruiming en serumfosfor moet by alle pasiënte uitgevoer word (sien **"KONTRA-INDIKASIES"**, **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**, **"Nierontoereikendheid"**).

NEWE-EFFEKTE

Newe-effekte aangemeld vir TYRICTEN 200/300 mg:

Bloed- en limfstelselafwykings:
Dikwels: Neutropenie.
Frekwensie onbekend: Anemie.

Immuunstelselafwykings:
Dikwels: Allergiese reaksie, waaronder angio-edeem.

Metabolisme en voedingsafwykings:
Dikwels: Hipertrigliseridemie, hiperglukemie.
Frekwensie onbekend: Hipofosfatemie, melksuurasidose, hipokalemie.

Psigiatriese afwykings:
Dikwels: Slaaploosheid, abnormale drome, depressie.

Senuweestelselafwykings:
Dikwels: Duiseligheid, hoofpyn, neuritis, parestesie, perifere neuropatie.

Respiratoriese-, bors en mediastinale afwykings:
Dikwels: Dispnee, toename in hoes, rinitis, borspyn, pneumonie.

Gastroïntestinale afwykings:
Dikwels: Diarree, naarheid, braking, winderigheid, sooibrand, buikpyn, verhoogde amilase, verhoogde lipase.
Frekwensie onbekend: Pankreatitis.

Hepatobiliêre afwykings:
Dikwels: Hiperbilirubinemie, verhoogde lewerensieme (waaronder verhoogde AST, verhoogde ALT en/of gamma-GT).
Frekwensie onbekend: Hepatitis, hepatiese steatose.

Vel- en subkutane weefselafwykings:
Dikwels: Uitslag gebeure (uitslag, pruritus, makulopapulêre uitslag, urtikarie, blaasagtige veluitslag, pustulêre uitslag), velverkleuring, hiperpigmentasie.

Muskuloskeletale-, bindweefsel en beenafwykings:
Dikwels: Kreatienkinase verhoog.
Frekwensie onbekend: Miopatie, osteomalasie (beide geassosieer met proksimale renale tubulopatie), rabdomiolise, spierswakheid.

Nier- en urienwegafwykings:
Frekwensie onbekend: Verhoogde kreatinien, renale ontoereikendheid, nierversaking, akute nierversaking, Fanconi se sindroom, proksimale tubulopatie, nefrogeniese diabetes insipidus, proteïenurie, akute tubulêre nekrose, poliurie, interstisiële nefritis (waaronder ook akute gevalle).

Algemene siektes en toestande by die plek van toediening:
Dikwels: Pyn, astenie, koors, sweet, gewigsverlies.

Newe-effekte wat vir emtrisitabien (200 mg) aangemeld is:

Senuweestelselafwykings:
Frekwensie onbekend: Depressie, neuropatie, perifere neuritis, parestesie.

Muskuloskeletale-, bindweefsel en beenafwykings:
Frekwensie onbekend: Artralgie, mialgie.

Respiratoriese-, bors en mediastinale afwykings:
Frekwensie onbekend: Hoes en rinitis neem toe.

Newe-effekte aangemeld vir Tenofovir (300 mg):

Gastroïntestinale afwykings:
Dikwels: Anoreksie.

Senuweestelselafwykings:
Frekwensie onbekend: Depressie, perifere neuropatie (waaronder perifere neuritis en neuropatie), angs.

Muskuloskeletale-, bindweefsel en beenafwykings:
Frekwensie onbekend: Rugpyn, mialgie, artralgie.

Respiratoriese-, bors en mediastinale afwykings:
Frekwensie onbekend: Borspyn, pneumonie.

Nier- en urienwegafwykings:
Frekwensie onbekend: Hematurie.

Algemene siektes en toestande by die plek van toediening:
Frekwensie onbekend: Koors, sweet, gewigsverlies.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN

By oordosis sal die newe-effekte vererger en oordrewe reaksies sal volg.

Indien oordosis voorkom moet die pasiënt vir tekens van toksisiteit gemoniteer word, en standaard ondersteunende behandeling moet soos nodig toegepas word.

Emtrisitabien: Daar bestaan beperkte kliniese ondervinding by dosisse wat hoër is as die terapeutiese dosis van emtrisitabien (200 mg).

Hemodialise verwyder ongeveer 30 % van die emtrisitabien dosis oor 'n 3-uur dialiseperiode, met aanvang binne 1,5 uur na dosering met emtrisitabien, (bloedvloei tempo van 400 ml/min en dialise vloeitempo van 600 ml/min). Dit is nie bekend of emtrisitabien met peritoneale dialise verwyder kan word nie.

Tenofovirdisoproksielfumaraat: Daar bestaan beperkte kliniese ondervinding by dosisse wat hoër is as die terapeutiese dosis van tenofovir 300 mg. Die effekte van hoër dosisse is nie bekend nie. Tenofovir word swak deur hemodialise verwyder. Na 'n enkeldosis van 300 mg tenofovir DF het 'n hemodialise sessie van 4 uur ongeveer 10 % van die toegediende dosis van tenofovir verwyder.

IDENTIFIKASIE

Wit tot naaswit, gemodifiseerde kapsuulvormige, filmbedekte tablette, met "I" op die een kant en "37" op die ander kant gedruk.

AANBIEDING

HDPE Houerverpakking:

Tablette word in wit, ondeursigtige, ronde HDPE houers met 'n 38 mm wit ondeursigtige polipropileen peuterbestande sluiting met 'n prop met 'n induksieseëlvoering, wat een 3 g silikajelsakkie bevat, verpak. Die HDPE houer sal verder verpak word in 'n voorafgedrukte karton met 'n verpakkingsbiljet.

Pakgrootte: 30's - Een HDPE-houer bevat 30 tablette.

BEWARINGSINSTRUKSIES

Bewaar by of benede 30 °C. Hou die houer dig toe.

Moet nie gebruik as die seël wat die houer bedek gebreek is, of nie teenwoordig is nie.

HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER

44/20.2.8/0086

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE

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P1519793

PASIËNTINLIGTINGSBILJET

SKEDULERINGSTATUS

S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM

TYRICTEN 200/300 mg (Emtrisitabien/Tenofovirdisoproksielfumaraat) Tablet

Lees die hele biljet deeglik deur voordat jy TYRICTEN 200/300 mg begin neem.

- Hou hierdie biljet. Dit is moontlik dat jy dit weer sal wil deurlees.
- Indien jy nog vrae het, raadpleeg asseblief jou dokter of apteker.
- **TYRICTEN 200/300 mg** is vir jou persoonlik voorgeskryf en jy moet nie jou medisyne met ander mense deel nie. Dit kan skadelik vir hulle wees, selfs al is hulle simptome dieselfde as joune.

WAARSKUWING

TYRICTEN 200/300 mg KAN LEI TOT ERNSTIGE PROBLEME MET JOU LEWER, OF TE VEEL SUUR IN JOU BLOED VEROORSAAK. INDIEN DIT NIE BEHANDEL WORD NIE, KAN DIT DOOD VEROORSAAK (SIEN "WEES VERSIGTIG MET TYRICTEN 200/300 mg").

TYRICTEN 200/300 mg WORD NIE VIR DIE BEHANDELING VAN CHRONIESE HEPATITIS B-VIRUS (HBV) AANGEDUI NIE EN DIE VEILIGHEID EN DOELTREFFENDHEID VAN TYRICTEN 200/300 mg IS NIE BY PASIËNTE WAT BEIDE MET MENS-IMMUUNGEBREKVIRUS (MIV) EN HEPATITIS B-VIRUS (HBV) BESMET IS, VASGESTEL NIE. JY MOET VIR ETLIKE MAANDE LANK ONDER DEEGLIKE TOESIG VAN JOU DOKTER WEES AS JY DIE GEBRUIK VAN TYRICTEN 200/300 mg STAAK EN JY MET BEIDE HBV EN MIV BESMET IS. INDIEN GEPAS, SAL JOU DOKTER DALK ANTI-HEPATITIS B BEHANDELING VOORSKRYF.

TYRICTEN 200/300 mg GEBRUIK VIR PRE-BLOOTSTELLING PROFILAKSE (PrEP) SAL SLEGS AAN JOU VOORGESKRYF WORD AS DIT BEVESTIG KON WORD DAT JY HIV-NEGATIEF IS, ONMIDDELLIK VOOR JY BEGIN OM TYRICTEN 200/300 mg TE GEBRUIK EN TEN MINSTE EEN KEER ELKE 3 MAANDE TERWYL JY TYRICTEN 200/300 mg GEBRUIK.

JY MOET NIE TYRICTEN 200/300 mg VIR PRE-BLOOTSTELLING PROFILAKSE (PrEP) NEEM AS JY TEKENS OF SIMPTOME VAN AKUTE MIV-1 INFEKSIE HET NIE, TENSY 'n NEGATIEWE INFEKSIESTATUS BEVESTIG IS.

INDIEN JY ALREEDS MIV HET, OF MIV OPDOEN EN JY NEEM TYRICTEN 200/300 mg VIR PRE-BLOOTSTELLING PROFILAKSE (PrEP), KAN DIE MIV VIRUS WEERSTANDIGHEID TEEN TYRICTEN 200/300 mg ONTWIKKEL EN MOEILIKER WORD OM TE BEHANDEL.

1. WAT TYRICTEN 200/300 mg BEVAT

Die aktiewe bestanddele is emtrisitabien en tenofovirdisoproksielfumaraat.

Elke filmbedekte tablet bevat 200 mg emtrisitabien en 300 mg tenofovirdisoproksielfumaraat.

Die ander bestanddele is: Natriumkroskarmellose, magnesiumstearaat, mikrokristallyne sellulose, pre-gelatineerde stysel en Opadry II Wit 32K18425 IH.

Die Opadry II Wit 32K18425 IH bevat: Hipromellose, laktosemonohidraat, titaandioksied (C.I. No: 77891), en triasetien.

Die tablette bevat suiker: Laktosemonohidraat 92,2 mg.

Belangrike inligting oor sommige bestanddele van TYRICTEN 200/300 mg

TYRICTEN 200/300 mg bevat laktose. Pasiënte met die rare oorerflike kondisies van laktose of galaktose intoleransie moet nie **TYRICTEN 200/300 mg** neem nie.

Laktose kan 'n effek hê op die beheer van u bloedsuiker indien u diabetes mellitus het.

2. WAARVOOR TYRICTEN 200/300 mg GEBRUIK WORD

TYRICTEN 200/300 mg is 'n tipe medisyne wat bekend staan as 'n MIV (Mens-Immuungebrek-Virus) nukleosiedanaloog trutranskriptaseremmer (NRTI). **TYRICTEN 200/300 mg** bevat twee aktiewe bestanddele, emtrisitabien (200 mg) en tenofovirdisoproksielfumaraat (of tenofovir DF) (300 mg), gekombineer in een tablet.

Elkeen van hierdie aktiewe bestanddele, ook bekend as antiretrovirale medisyne, werk deur in te gryp op 'n ensiem (trutranskriptase) wat noodsaaklik is vir die virus om te vermenigvuldig.

BEHANDELING MET TYRICTEN 200/300 mg VOORKOM NIE OORDRAG VAN MIV NIE.

Vir die behandeling van MIV-infeksie:

TYRICTEN 200/300 mg word gebruik by volwassenes in kombinasie met ander medisyne teen MIV, om mense met MIV-infeksie te behandel.

Behandeling vir Pre-Blootstelling Profilakse (PrEP)

Om by volwassenes die risiko om MIV-1 op te doen te verminder, moet **TYRICTEN 200/300 mg** streng in kombinasie met veiliger sekspraktyke gebruik word en moet daar ook te alle tye streng gehou word by die gebruik daarvan. Dit staan bekend as Pre-Blootstelling Profilakse, of PrEP.

3. VOORDAT JY TYRICTEN 200/300 mg NEEM

Moenie TYRICTEN 200/300 mg neem nie:

- As jy hipersensitief (allergies) is vir emtrisitabien, tenofovirdisoproksielfumaraat, of vir enige van die ander bestanddele van **TYRICTEN 200/300 mg** nie.
- Indien jy nierprobleme het, of as jy dialise ondergaan.
- Indien jy swanger is of borsvoed.
- Indien jy reeds ander medisyne neem wat tenofovir of emtrisitabien bevat, of medisyne wat lamivudien bevat, want hierdie medisyne bevat dieselfde of vergelykbare aktiewe bestanddele.
- Indien jy 'n vrou is wat **TYRICTEN 200/300 mg** neem om MIV-infeksie te voorkom en jy swanger raak terwyl jy **TYRICTEN 200/300 mg** neem**.**
- Indien jy MIV-positief is, of as jou MIV status nie bekend is nie, moet jy nie **TYRICTEN 200/300 mg** neem om MIV-infeksie te voorkom nie.
- Indien jy nie volkome toegewy is aan die daaglikse gebruik van **TYRICTEN 200/300 mg** vir Pre-Blootstelling Profilakse nie.

Sien die afdeling "WAARVOOR TYRICTEN 200/300 mg GEBRUIK WORD" en praat met jou gesondheidsorgkundige om meer inligting te kry oor hoe om MIV-infeksie te voorkom.

Wees versigtig met TYRICTEN 200/300 mg:

TYRICTEN 200/300 mg kan lei tot ernstige probleme met jou lewer, of te veel suur in jou bloed veroorsaak. Indien dit nie behandel word nie, kan dit die dood veroorsaak. Die veiligheid en doeltreffendheid van TYRICTEN 200/300 mg is nie by pasiënte wat beide die mens-immuungebrekvirus (MIV) en hepatitis B-virus (HBV) besmet is, vasgestel nie. TYRICTEN 200/300 mg moet nie gebruik word vir die behandeling van chroniese HBV-infeksie nie. Jy moet vir etlike maande lank onder deeglike toesig van jou dokter wees as jy die HBV-infeksie het en jy die gebruik van TYRICTEN 200/300 mg staak.

- **TYRICTEN 200/300** kan melksuurasidose veroorsaak, wat tesame met 'n vergrote lewer, noodlottig kan wees. Diep, vinnige asemhaling, lomerigheid, en nie-spesifieke simptome soos naarheid, braking en maagpyn kan dui op die ontwikkeling van melksuurasidose. Melksuurasidose kom meer dikwels by vrouens voor, veral as hulle oorgewig is.
  Lig jou dokter in as jy lewersiekte het (waaronder hepatitis B). **TYRICTEN 200/300 mg** moet nie gebruik word om hepatitis B virusinfeksie (HBV; 'n voortslepende lewerinfeksie) te behandel nie. Lig jou dokter in as HBV het, of dink dat jy dit kan hê. Jou dokter kan jou toets om te sien of jy HBV het, voordat jy begin met jou behandeling met **TYRICTEN 200/300 mg**. Indien jy HBV het en jy neem **TYRICTEN 200/300 mg**, kan jou toestand skielik versleg as jy ophou om **TYRICTEN 200/300 mg** te neem. Jou dokter sal jou ondersoek en gereeld laboratoriumtoetse aanvra vir etlike maande nadat jy opgehou het om **TYRICTEN 200/300 mg** te neem, om te sien of jou HBV erger geword het.
  Lig jou dokter in as jy 'n niersiekte het, of as toetse wys dat jy nierprobleme het. **TYRICTEN 200/300 mg** kan jou niere aantas. Voordat jy behandeling begin, kan jou dokter bloedtoetse aanvra om die werking van jou niere te bepaal. Jou dokter kan ook bloedtoetse aanvra tydens die behandeling om jou niere te moniteer.
- **TYRICTEN 200/300 mg** word gewoonlik nie saam met ander medisyne geneem wat jou niere kan beskadig nie. Indien dit onvermydelik is, sal jou dokter jou nierfunksie moniteer.
- Beenprobleme: Sommige pasiënte wat kombinasie antiretrovirale behandeling kry, kan 'n beensiekte ontwikkel. Jou dokter kan oorweeg om jou bene dop te hou as jy 'n geskiedenis het van 'n beenbreuk, of 'n risiko loop vir osteopenie ('n toestand waar die beenmineraaldigtheid laer is as die normale).
- **TYRICTEN 200/300 mg** kan jou liggaamsvorm verander, deur die manier waarop die liggaamsvet versprei word, te verander. Jy kan vet uit jou bene, arms en gesig verloor; vet om die maag en inwendige organe aanpak; groter borste kry, of vetagtige bulte agter op die nek (buffelskof). Die oorsaak en langtermyneffek van hierdie veranderinge is nog nie bekend nie.
- **TYRICTEN 200/300 mg** is nie bestudeer by pasiënte ouer as 65 jaar nie. Indien jy ouer as dit is en **TYRICTEN 200/300 mg** aan jou voorgeskryf word, sal jou dokter deeglik toesig oor jou hou.
- Die veiligheid en doeltreffendheid van **TYRICTEN 200/300 mg** is nie by kinders en adolessente bepaal nie.
- Enige kind wat al in die baarmoeder aan **TYRICTEN 200/300 mg** blootgestel word, selfs MIV-negatiewe kinders, moet klinies en met laboratoriumtoetse opgevolg word en moet volledig ondersoek word vir moontlike mitochondriese disfunksie.
- Wees bedag op infeksies. Indien jy gevorderde MIV-infeksie (VIGS) het en 'n infeksie ontwikkel, kan jy simptome van infeksie of ontsteking, of agteruitgang van simptome, of 'n bestaande infeksie ontwikkel sodra behandeling met **TYRICTEN 200/300 mg** begin word. Indien jy tekens van ontsteking of infeksie opmerk, sê dadelik jou dokter daarvan.
- Indien jy ander medisyne neem, want **TYRICTEN 200/300 mg** kan 'n interaksie met ander medisyne hê.
- Indien jy diabeties of oorgewig is, of as jy hoë cholesterol het, praat met jou dokter daaroor.

Ander belangrike inligting waarvan jy moet weet voordat jy begin met TYRICTEN 200/300 mg vir die behandeling van MIV-1:

- Jy moet deurentyd op MIV behandeling bly om MIV-infeksie te beheer en om MIV-verwante siektes te verminder.
- **TYRICTEN 200/300 mg genees nie MIV nie**. Indien jy alreeds MIV het, of MIV opdoen en jy neem slegs **TYRICTEN 200/300 mg** sonder enige ander medisyne, kan jy weerstandigheid teen **TYRICTEN 200/300 mg** ontwikkel. Dit beteken dat dit moeiliker kan word om die MIV virus te behandel.
- **TYRICTEN 200/300 mg** verminder nie jou kans om MIV deur seksuele kontak, deel van naalde, of blootstelling aan jou bloed, aan ander mense oor te dra nie. Vir jou gesondheid en die gesondheid van ander mense is dit belangrik dat jy altyd veilige seks beoefen.
- Jy kan steeds opportunistiese infeksies kry, of ander siektetoestande opdoen wat met MIV-infeksie gebeur. Opportunistiese infeksies is infeksies wat ontwikkel omdat die immuunstelsel swak is.

Sommige van hierdie siektetoestande is verskillende vorms van tuberkulose infeksie, 'n vorm van longontsteking, herpes virusinfeksies en 'n vorm van meningitis (infeksie van die beskermende membrane om die brein en rugmurg).

Ander belangrike inligting om van kennis te neem voordat jy TYRICTEN 200/300 mg neem, om te help keer dat jy MIV kry:

- **Jy moet getoets word om seker te maak jy is MIV-negatief.** Dit is belangrik dat jy ook ten minste elke 3 maande, soos aanbeveel deur jou gesondheidsorgkundige, getoets word terwyl jy **TYRICTEN 200/300 mg** neem. Vra jou seksuele vennoot om ook getoets te word. Wees bewus van die MIV status van jou vennoot.
- **TYRICTEN 200/300 mg** sal moontlik nie altyd verhoed dat jy MIV kry nie.
- **Jy moet steeds ten alle tye veilige seks beoefen. Moenie enige soort seks sonder beskerming hê nie.** Beoefen altyd veilige seks deur 'n lateks of poliuretaan kondoom te gebruik om die kans vir seksuele kontak met semen, vaginale sekresies of bloed, te verlaag.
- **Jy moet ook ander metodes van voorbehoeding gebruik om te keer dat jy MIV kry.**
- Kry inligting daaroor en ondersteuning om te help om riskante seksuele gedrag te verminder.
- Beperk die aantal seksuele vennote.
- **Moenie enige dosisse TYRICTEN 200/300 mg oorslaan nie. As jy dosisse oorslaan verhoog jy jou kans om MIV op te doen.**

Ander belangrike inligting om van kennis te neem voordat jy TYRICTEN 200/300 mg neem, om te help keer dat jy MIV opdoen, of om meer te weet oor die MIV-1 behandeling:

Vermy aktiwiteite wat jou risiko van die verspreiding van MIV-infeksie aan ander mense kan verhoog as jy met MIV besmet is, of wat jou risiko vir die verkryging van MIV kan verhoog, as jy **TYRICTEN 200/300 mg** vir voorkoming neem.

Dit behels:

- Moenie naalde of ander toerusting vir inspuiting deel of hergebruik nie.
- Moenie persoonlike items wat bloed of liggaamsvloeistowwe bevat, soos tandeborsels of skeermeslemmetjies, deel nie.
- Moenie enige soort seks sonder beskerming hê nie. Beoefen altyd veilige seks deur 'n lateks of poliuretaan kondoom te gebruik om die kans vir seksuele kontak met semen, vaginale sekresies of bloed, te verlaag.

Lig jou gesondheidsorgkundige in as jy enige van die volgende simptome oor die afgelope maand gehad het, voordat jy begin om **TYRICTEN 200/300 mg** te neem, of te eniger tyd terwyl jy **TYRICTEN 200/300 mg** neem:

- moegheid
- koors
- sweet baie (veral snags)
- uitslag
- braking
- diarree
- pyn in die gewrigte of spiere
- hoofpyn
- seer keel
- vergrote limfknope in die nek of lies.

Dit kan tekens wees van MIV- infeksie en dit kan nodig wees dat jy nog 'n toets moet ondergaan om MIV te diagnoseer.

Lig ook jou gesondheidsorgkundige in as jy dink dat jy onlangs aan die MIV virus blootgestel is. Indien jy reeds **TYRICTEN 200/300 mg** neem om te verhoed dat jy MIV-1 infeksie kry, kan jou gesondheidsorgkundige jou aanraai om op te hou om **TYRICTEN 200/300 mg** te neem, totdat 'n MIV-toets bevestig het dat jy nie MIV-1 infeksie het nie.

Neem van TYRICTEN 200/300 mg met kos en vloeistof:

TYRICTEN 200/300 mg kan met of sonder voedsel geneem word. Neem **TYRICTEN 200/300 mg** elke dag op dieselfde tyd.

Swangerskap en borsvoeding:

- Jy moet nie **TYRICTEN 200/300 mg** tydens swangerskap neem nie. Die effek van **TYRICTEN 200/300 mg** op swanger vrouens of hulle ongebore babas is onbekend.
- 'n Betroubare metode van voorbehoeding moet gebruik word om swangerskap te vermy terwyl **TYRICTEN 200/300 mg** geneem word.
- Moenie borsvoed tydens behandeling met **TYRICTEN 200/300 mg** nie. Moenie borsvoed as jy MIV het nie. Dit is nie bekend of die aktiewe bestanddele in hierdie medisyne in die borsmelk uitgeskei word nie. Indien jy 'n vrou is wat 'n baba het, of gaan hê, praat met jou gesondheidsorgkundige oor die beste manier om jou baba te voed.
- Indien jy 'n vrou is wat MIV het word dit aanbeveel dat jy nie borsvoed nie, om te voorkom dat jy die virus deur die borsmelk aan jou baba oordra. Indien jou baba nie reeds MIV het nie, is daar 'n kans dat die baba MIV deur borsvoeding kan kry.

Indien jy swanger is, of jou baba borsvoed, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgkundige vir advies voordat jy **TYRICTEN 200/300 mg** neem.

Bestuur en gebruik van masjinerie:

TYRICTEN 200/300 mg kan duiseligheid veroorsaak. Moenie bestuur of enige gereedskap of masjinerie gebruik as jy duiselig voel nie.

Neem van ander medisyne saam met TYRICTEN 200/300 mg:

Lig altyd jou gesondheidsorgkundige in as jy enige ander medisyne neem. (Dit sluit komplementêre of tradisionele medisynes in.)

- Jy moet nie **TYRICTEN 200/300 mg** neem as jy reeds ander medisyne neem wat emtrisitabien, tenofovirdisoproksielfumaraat of lamivudien bevat nie. **TYRICTEN 200/300 mg moet nie saam met dié medisyne gebruik word nie, omdat hulle dieselfde of soortgelyke aktiewe bestanddele as TYRICTEN 200/300 mg bevat (sien "MOENIE TYRICTEN 200/300 mg NEEM NIE").**
- Lig jou dokter in as jy atasanavir en/of lopinavir/ritonavir neem: As jy enige van hierdie medisyne neem, sal jou dokter jou behandeling meer noukeurig wil dophou en dit is moontlik dat jy nie **TYRICTEN 200/300 mg** sal kan gebruik nie.
- Lig jou dokter in as jy enige medisyne neem wat didanosien (vir MIV-infeksie) bevat. As jy **TYRICTEN 200/300 mg** saam met ander antivirale medisynes neem wat didanosien bevat, sal dit die konsentrasie van didanosien in jou bloed verhoog. Ontsteking van die pankreas en neuropatie (senuwee-aantasting) kan voorkom. Jou dokter sal sorgvuldig oorweeg om jou met kombinasies van tenofovir en didanosien te behandel.

Lig jou dokter in as jy enige ander medisyne neem wat jou nierfunksie kan verswak. 'n Paar voorbeelde is, onder andere, adefovirdipivoksiel, sidofovir, asiklovir, valasiklovir, gansiklovir en valgansiklovir.

Hou volledig rekord van al die medisyne wat jy neem. Maak 'n nuwe lysie as daar van die medisyne bygevoeg of gestaak word. Gee elke keer wat jy 'n gesondheidsorgkundige of apteker besoek, of 'n voorskrif vir medisyne ingee, aan hulle 'n afskrif van hierdie lys.

4. HOE OM TYRICTEN 200/300 mg TE NEEM

Moenie medisyne wat vir jou voorgeskryf is met 'n ander persoon deel nie.

Neem **TYRICTEN 200/300 mg** altyd presies soos jou dokter dit vir jou voorgeskryf het. As jy onseker is, vra jou dokter of apteker. Indien jy die indruk kry dat die effek van **TYRICTEN 200/300 mg** te sterk of te swak is, lig jou dokter of apteker in.

Aanbevole dosering van TYRICTEN 200/300 mg:

Die gewone volwasse dosis is een tablet een keer daagliks, met of sonder kos geneem. Neem **TYRICTEN 200/300 mg** elke dag op dieselfde tyd.

Behandeling van MIV:

As jy **TYRICTEN 200/300 mg** vir die behandeling van MIV-infeksie neem, moet dit in kombinasie met ander anti-MIV-medisyne gebruik word.

Voorkoming van MIV:

Indien jy TYRICTEN 200/300 mg neem om die risiko vir MIV-1 te verminder, moet jy ook ander metodes gebruik om jou risiko vir MIV te verminder. Sien "Wees versigtig met TYRICTEN 200/300 mg".

Jou dokter sal jou inlig hoe lank jou behandeling met **TYRICTEN 200/300 mg** sal aanhou. Moenie jou behandeling voortydig staak nie.

Indien jy meer TYRICTEN 200/300 mg geneem het as wat jy moes:

In die geval van 'n oordosering, raadpleeg jou dokter of apteker. Indien geeneen beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.

Indien jy vergeet om TYRICTEN 200/300 mg te neem:

Dit is belangrik dat jy nie enige dosisse oorslaan nie. As jy vergeet het om 'n dosis te neem, neem dit sodra jy daarvan onthou en gaan aan soos voorheen. Moenie 'n dubbele dosis neem om op te maak vir vergete individuele dosisse nie. Kontak jou gesondheidsorgkundige of apteker as jy nie seker is wat om te doen nie. Moenie meer as een **TYRICTEN 200/300 mg** op 'n dag neem nie.

Effekte wanneer behandeling met TYRICTEN 200/300 gestaak word

Jy moet nie jou behandeling staak nie, tensy jou dokter so sê nie. Wanneer jou voorraad **TYRICTEN 200/300 mg** laag raak, vul dit aan by jou gesondheidsorgkundige of apteek. Dit is baie belangrik, want die aantal virusse in jou bloed kan vermeerder as die medisyne selfs vir 'n kort rukkie gestaak word. Die virus kan weerstandigheid tot **TYRICTEN 200/300 mg** ontwikkel en moeilik raak om te behandel.

5. MOONTLIKE NEWE-EFFEKTE

TYRICTEN 200/300 mg kan newe-effekte hê.

Nie alle newe-effekte wat vir **TYRICTEN 200/300 mg** aangemeld is, word in hierdie biljet genoem nie. Indien jou algemene gesondheid agteruitgaan of jy enige ongunstige effekte ervaar terwyl jy **TYRICTEN 200/300 mg** neem, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgkundige vir advies.

Indien enige van die volgende gebeur, staak TYRICTEN 200/300 mg en lig dadelik jou dokter in, of gaan na die ongevalle-afdeling by jou naaste hospitaal:

- Swelling van die hande, voete, enkels, gesig, lippe, mond of keel, wat probleme om te sluk of asem te haal kan veroorsaak (angio-edeem);
- uitslag of jeuk;
- floute.

Hierdie is almal baie ernstige newe-effekte. Indien jy dit ervaar, kan jy moontlik 'n ernstige allergiese reaksie op **TYRICTEN 200/300 mg** ervaar. Jy kan dringende mediese aandag of hospitalisering benodig.

Lig jou dokter dadelik in as jy enige van die volgende tekens waarneem, of gaan na die ongevalle-afdeling by jou naaste hospitaal:

- Moeilike asemhaling;
- minder urine as normaalweg;
- tekens of simptome van melksuurasidose (opbou van suur in die bloed) bv. jy voel swak of moeg, jy het ongewone spierpyn, jy haal moeilik asem, jy het maagpyn met naarheid en braking, jy voel koud (veral in jou arms en bene), duiselig en lighoofdig en het 'n vinnige of onreëlmatige hartklop;
- tekens of simptome van ernstige lewerprobleme, bv. die vel of oogwitte word geel (geelsug), urine word donker gekleurd, stoelgange word lig gekleurd, jy voel siek op jou maag (naarheid), jy het laer maagpyn (buikpyn) en voel vir 'n paar dae of langer nie lus om te eet nie;
- tekens van versagting van die bene (beenpyn en soms lei dit tot beenbreuke).

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

Lig jou dokter in as jy enige van die volgende waarneem:

Die volgende newe-effekte is dikwels aangemeld:

- Maagpyn;
- pyn;
- abnormale fisiese swakheid of gebrek aan energie;
- diarree;
- hoofpyn;
- spelde-en-naalde gevoel; ontsteking van die senuwees wat pyn veroorsaak;
- hoes meer, loopneus, pneumonie (longinfeksie);
- borspyn;
- naarheid (naar gevoel), braking;
- duiseligheid;
- probleme om te slaap, abnormale drome, depressiewe gemoedstoestand;
- probleme met spysvertering wat lei tot ongemak na maaltye, opgeblase gevoel, winderigheid;
- uitslag (waaronder rooi kolle of vlekke, soms met blase en swelling van die vel wat allergiese reaksies kan wees), jeuk, veranderinge in velkleur insluitend donker vlekke op die vel;
- ander allergiese reaksies bv. hyging, swelling of lighoofdigheid;
- koors, sweet, gewigsverlies;
- eetstoornis.

Bloedtoetse kan ook toon:

- 'n Lae witbloedseltelling ('n lae witbloedseltelling kan jou meer vatbaar maak vir infeksie);
- verhoogde trigliseriede (vetsure), gal of suiker in die bloed;
- verhoogde kreatienkinase ('n ensiem wat geproduseer word deur die afbraak van jou spiere);
- verhoogde amilase of lipase in die bloed;
- verhoogde lewerensieme.

Die volgende newe-effekte is aangemeld, maar die voorkoms is onbekend:

- Rugpyn, veroorsaak deur nierprobleme;
- anemie (lae rooibloedseltelling), wat simptome kan insluit soos moegheid, bleek vel, kortasem, lighoofdigheid, duiseligheid, of 'n vinnige hartklop;
- afbraak van spiere, spierpyn of swakheid wat kan voorkom vanweë beskadiging aan die selle in die nierbuisies;
- ontsteking van die pankreas wat heel dikwels begin met buikpyn in die middel of linker-boonste deel van die buik, en wat erger kan word na etes, of as jy plat op jou rug lê.

Bloed- en urientoetse kan ook toon:

- Afnames in kalium in die bloed;
- afnames in fosfaat in die bloed;
- verhoogde kreatinien in jou bloed;
- veranderinge in jou urine.

Hierdie lys van newe-effekte is nie volledig nie. Indien jy vrae het oor newe-effekte, praat met jou gesondheidsorgkundige. Jy moet enige nuwe of aanhoudende simptome dadelik aan jou gesondheidsorgkundige meedeel. Jou gesondheidsorgkundige kan jou help om hierdie newe-effekte te beheer. Indien jy enige newe-effekte waarneem wat nie in hierdie biljet vermeld word nie, lig jou dokter of apteker in.

6. BEWARING EN WEGDOENING VAN TYRICTEN 200/300 mg

Bewaar teen of benede 30 °C (kamertemperatuur). Hou die houer dig toe.

Moenie gebruik as die seël wat die houer bedek, gebreek of nie teenwoordig is nie.

HOU ALLE MEDISYNE BUITE BEREIK VAN KINDERS.

Neem alle ongebruikte medisyne terug na jou apteker.

Moenie ongebruikte medisyne in afvoerpype of rioolstelsels (bv. toilette) gooi nie.

7. AANBIEDING VAN TYRICTEN 200/300 mg

HDPE verpakking:

Tablette word in wit, ondeursigtige, ronde HDPE houers met 'n 38 mm wit ondeursigtige polipropileen peuterbestande sluiting met 'n prop met 'n induksieseëlvoering, wat een 3 g silikajelsakkie bevat, verpak.

Die HDPE houer sal verder verpak word in 'n voorafgedrukte karton met 'n verpakkingsbiljet.

Pakgrootte: 30's - Een HDPE-houer bevat 30 tablette.

8. IDENTIFIKASIE VAN TYRICTEN 200/300 mg

Wit tot naaswit, gemodifiseerde kapsuulvormige, filmbedekte tablette, met "I" op die een kant en "37" op die ander kant gedruk.

9. REGISTRASIENOMMER

44/20.2.8/0086

10. NAAM, BESIGHEIDSADRES EN TELEFOONNOMMER VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE

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11. DATUM VAN PUBLIKASIE

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Datum van mees onlangse goedkeuring deur die Raad: 6 April 2017