ZEFIN 300 mg TABLETS
P1526405

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PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ZEFIN 300 mg TABLETS (Tablet)

COMPOSITION:
Each film-coated tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil.
Excipients: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch.
The coating Opadry II White contains: Hypromellose, lactose monohydrate, titanium dioxide (C.I. No: 77891), and triacetin.
Contains sugar: Lactose 120,83 mg.

> **WARNING:**
> **LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF ZEFIN 300 mg TABLETS OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE "WARNINGS AND SPECIAL PRECAUTIONS ").**
> **ZEFIN 300 mg TABLETS IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF ZEFIN 300 mg TABLETS HAS NOT BEEN ESTABLISHED IN PATIENTS CO-INFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HBV AND HIV AND HAVE DISCONTINUED ZEFIN 300 mg TABLETS. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ZEFIN 300 mg TABLETS AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE "WARNINGS AND SPECIAL PRECAUTIONS").**

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.8. Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents.

PHARMACOLOGICAL ACTION:

Mechanism of Action:
Tenofovir disoproxil fumarate 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 reverse transcriptase 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.

Medicine Resistance:
HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2 - 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. In treatment-naïve patients treated with tenofovir + lamivudine + efavirenz, viral isolates from 8/47 (17 %) patients with virologic failure showed reduced susceptibility to tenofovir. In treatment-experienced patients, 14/304 (4,6 %) of the tenofovir-treated patients with virologic failure through week 96 showed reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a mutation in the HIV-1 reverse transcriptase gene resulting in the K65R amino acid substitution.

Cross-resistance:
Cross-resistance among certain reverse transcriptase inhibitors has been recognised. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these medicines may occur in patients whose virus harbours the K65R mutation. HIV-1 isolates from patients (N = 20) whose HIV-1 expressed a mean of 3 zidovudine - associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N), showed a 3,1 - fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

Pharmacodynamic properties:
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.
The IC_{50} (50 % inhibitory concentration) values for tenofovir were in the range of 0,04 – 8,5 μM. 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 (IC_{50} values ranged from 0,5 – 2,2 M). The IC_{50} values of tenofovir against HIV-2 ranged from 1,6 M to 4,9 M.

Pharmacokinetic properties:
The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption:
Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients is approximately 25 %. Following oral administration of a single dose of tenofovir 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1,0 ± 0,4 hrs. C_{max} and AUC values are 296 ± 90 ng/ml and 2287 ± 685 ng*h/ml, respectively. The pharmacokinetics of tenofovir are dose proportional over a dose range of 75 to 600 mg and are not affected by repeated dosing.

Effects of Food on Oral Absorption:
Administration of tenofovir following a high-fat meal (~ 700 to 1 000 kcal containing 40 to 50 % fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40 % and an increase in C_{max} of approximately 14 %. However, administration of tenofovir with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the medicine. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ± 119 ng/ml and 3 324 ± 1 370 ng*h/ml, respectively, following multiple doses of tenofovir 300 mg once daily in the fed state, when meal content was not controlled.

Distribution:
In vitro binding of tenofovir to human plasma or serum proteins is less than 0,7 % and 7,2 %, respectively, over the tenofovir concentration range 0,01 to 25 μg/ml. The volume of distribution at steady-state is 1,3 ± 0,6 l/kg and 1,2 ± 0,4 l/kg, following intravenous administration of tenofovir 1,0 mg/kg and 3,0 mg/kg.

Metabolism and Elimination:
In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes. Following IV administration of tenofovir, approximately 70 – 80 % of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir 300 mg once daily (under fed conditions), 32 ± 10 % of the administered dose is recovered in urine over 24 hours.
Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations:
Tenofovir pharmacokinetics are similar in male and female patients. Pharmacokinetic studies have not been performed in children (< 18 years) or in the elderly (> 65 years).
The pharmacokinetics of tenofovir following a 300 mg single dose 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. No change in tenofovir dosing is required in patients with hepatic impairment.
The pharmacokinetics of tenofovir are altered in patients with renal impairment. In patients with creatinine clearance < 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased. It is recommended that the dosing interval for tenofovir be modified in patients with creatinine clearance < 50 mL/min or in patients with ESRD who require dialysis (see "**DOSAGE AND DIRECTIONS FOR USE**").
Tenofovir is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of tenofovir, a four-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

INDICATIONS:
ZEFIN 300 mg TABLETS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

CONTRAINDICATIONS:
ZEFIN 300 mg TABLETS is contraindicated in:
- Patients with previously demonstrated hypersensitivity to any of the components of the product.
- Moderate to severe renal failure.
- Pregnancy and lactation (see "**PREGNANCY AND LACTATION**").

WARNINGS and SPECIAL PRECAUTIONS:
There are no study results demonstrating the effect of **ZEFIN 300 mg TABLETS** on clinical progression of HIV-1.

Lactic acidosis/Hyperlactataemia/Severe hepatomegaly with steatosis:
Use of **ZEFIN 300 mg TABLETS** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction.
Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss.
In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/l) and serum bicarbonate and respond as follows:

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

Lactate 5 – 10 mmol/l with symptoms and/or with reduced standard bicarbonate: – STOP NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.

Lactate > 10 mmol/l - STOP all therapy (80 % mortality).
The above lactate values may not be applicable to paediatric patients.
Caution should be exercised when administering **ZEFIN 300 mg TABLETS** to patients with known risk factors for liver disease.
Treatment with **ZEFIN 300 mg TABLETS** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues such as **ZEFIN 300 mg TABLETS** 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 **ZEFIN 300 mg TABLETS** 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 **ZEFIN 300 mg TABLETS** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Mitochondrial dysfunction:
Nucleoside and nucleotide analogues such as **ZEFIN 300 mg TABLETS** 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 such as **ZEFIN 300 mg TABLETS**. 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 such as **ZEFIN 300 mg TABLETS**, 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.

Pancreatitis:
Pancreatitis has been observed in some patients receiving **ZEFIN 300 mg TABLETS**. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **ZEFIN 300 mg TABLETS** until diagnosis of pancreatitis is excluded.

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

Immune Reconstitution Inflammatory Syndrome:
Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination antiretroviral 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 tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.
Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Patients with moderate to severe renal impairment:
In patients with moderate to severe renal impairment, the terminal half-life of **ZEFIN 300 mg TABLETS** is increased due to decreased clearance. The dose of **ZEFIN 300 mg TABLETS** should therefore be adjusted (see "**DOSAGE AND DIRECTIONS FOR USE**").
Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphataemia), has been reported in association with the use of **ZEFIN 300 mg TABLETS**.

ZEFIN 300 mg TABLETS should be avoided with recent or concurrent use of a nephrotoxic agent. Patients at risk of, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

Liver disease:
Use of **ZEFIN 300 mg TABLETS** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **ZEFIN 300 mg TABLETS** has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant packaging leaflets for these medicines.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered.

Patients with HIV and hepatitis B or C virus co-infection:
It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral 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. **ZEFIN 300 mg TABLETS** is not indicated for the treatment of chronic HBV infection. The safety and efficacy of **ZEFIN 300 mg TABLETS** have not been established in patients co-infected with HBV and HIV.

Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

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

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

Discontinuation of **ZEFIN 300 mg TABLETS** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Medicine Interactions (See "INTERACTIONS"):
When administered with **ZEFIN 300 mg TABLETS**, C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increases significantly (see Table 3). 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 **ZEFIN 300 mg TABLETS**. Data are not available to recommend a dose adjustment of didanosine for patients weighing < 60 kg. When co-administered, **ZEFIN 300 mg TABLETS** and didanosine EC may be taken under fasted conditions or with a light meal (< 400 kcal, 20 % fat). Co-administration of didanosine buffered tablet formulation with **ZEFIN 300 mg TABLETS** should be under fasted conditions. **Co-administration of ZEFIN 300 mg TABLETS 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.**

Atazanavir and lopinavir/ritonavir have been shown to increase **ZEFIN 300 mg TABLETS** concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and lopinavir/ritonavir and **ZEFIN 300 mg TABLETS** should be monitored for **ZEFIN 300 mg TABLETS -** associated adverse events. **ZEFIN 300 mg TABLETS** should be discontinued in patients who develop **ZEFIN 300 mg TABLETS** - associated adverse events.

ZEFIN 300 mg TABLETS decreases the AUC and C_{min} of atazanavir. When co-administered with **ZEFIN 300 mg TABLETS**, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be co-administered with **ZEFIN 300 mg TABLETS.**

Since **ZEFIN 300 mg TABLETS** is primarily eliminated by the kidneys, co-administration of **ZEFIN 300 mg TABLETS** with medicines that reduce renal function or compete for active tubular secretion may increase serum concentrations of **ZEFIN 300 mg TABLETS** and/ or increase the concentrations of other renally eliminated medicines. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir and valganciclovir.

Higher **ZEFIN 300 mg TABLETS** concentrations could potentiate **ZEFIN 300 mg TABLETS** - associated adverse events, including renal disorders.

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

Bone Effects:
ZEFIN 300 mg TABLETS decreases bone mineral density.
Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Opportunistic infections:
Patients receiving **ZEFIN 300 mg TABLETS** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:
Patients should be advised that current antiretroviral therapy, including **ZEFIN 300 mg TABLETS**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Paediatric Use:
Safety and effectiveness in paediatric patients and patients < 18 years of age have not been established.

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

INTERACTIONS:
ZEFIN 300 mg TABLETS is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Co-administration of **ZEFIN 300 mg TABLETS** with medicines that are eliminated by active tubular secretion may increase serum concentrations of either **ZEFIN 300 mg TABLETS** or the co-administered medicine, due to competition for this elimination pathway. Medicines that decrease renal function may also increase serum concentrations of **ZEFIN 300 mg TABLETS**. Tenofovir as contained in **ZEFIN 300 mg TABLETS**, has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives, and ribavirin. Tables 1 and 2 summarise pharmacokinetic effects of co-administered medicine on **ZEFIN 300 mg TABLETS** pharmacokinetics and effects of **ZEFIN 300 mg TABLETS** on the pharmacokinetics of co-administered medicine.

Table 3 summarises the medicine interaction between **ZEFIN 300 mg TABLETS** and didanosine. When administered with multiple doses of **ZEFIN 300 mg TABLETS**, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules are administered with **ZEFIN 300 mg TABLETS**, systemic exposures to didanosine are similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 1: Medicine Interactions: Changes in Pharmacokinetic Parameters for ZEFIN 300 mg TABLETS[1] in the Presence of the Co-administered Medicine.

Co-administered Medicine	Dose of Co-administered Medicine (mg)	N	% Change of ZEFIN 300 mg TABLETS Pharmacokinetic Parameters[2] (90 % CI)		
			C_{max}	AUC	C_{min}
Abavacavir	300 once	8	<=>	<=>	NC
Adefovir dipivoxil	10 once	22	<=>	<=>	<=>
Atazanavir	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	13	↑14 (↓3 to ↑33)	<=>	<=>
Lamivudine	150 twice daily x 7 days	15	<=>	<=>	<=>
Lopinavir/ Ritonavir	400/100 twice daily x 14 days	24	<=>	↑32 (↑26 to ↑38)	↑29 (↑32 to ↑66)

1. Patients received **ZEFIN 300 mg TABLETS** 300 mg once daily
2. Increase = ↑; decrease = ↓; No Effect = <=>; NC = Not Calculated

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 **ZEFIN 300 mg TABLETS**.

Table 2: Medicine Interactions: Changes in Pharmacokinetic parameters for Co-administered Medicine in the Presence of ZEFIN 300 mg TABLETS.

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}
Abavacavir	300 once	8	↑12 (↓1 to ↑26)	<=>	NA
Adefovir dipivoxil	10 once	22	<=>	<=>	NA
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	Lopinavir/Ritonavir 400/100 twice daily x 14 days	21	<=>	<=>	<=>
Methadone[2]	40-110 once daily x 14 days[3]	13	<=>	<=>	<=>
Oral Contraceptives[4]	Ethinyl Estradiol/Norgestimate Once daily x 7 days	20	<=>	<=>	<=>
Ribavirin	600 once	22	<=>	<=>	NA
Ritonavir	Lopinavir/Ritonavir 400/100 twice daily x 14 days	24	<=>	<=>	<=>
Atazanavir	400 once daily x 14 days	34	↓21 (↓27 to ↓14)	↓25 (↓30 to ↓19)	↓40 (↓48 to ↓32)
Atazanavir	Atazanavir/Ritonavir 300/100 once daily x 42 days.	10	↓28 (↓50 to ↑5)	↓25 (↓42 to ↓3)	↓23[5] (↓46 to ↑10)

1. Increase = ↑; Decrease = ↓; No Effect = <=>; NA = Not Applicable
2. R-(active), S-and total methadone exposures were equivalent when dosed alone or with **ZEFIN 300 mg TABLETS**.
3. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
4. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with Z**EFIN 300 mg TABLETS**.
5. In HIV-infected patients, addition of TFD 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.

Table 3: Medicine Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of ZEFIN 300 mg TABLETS.

Didanosine[1] Dose (mg)/ Method of Administration[2]	ZEFIN 300 mg TABLETS 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 "PRECAUTIONS" regarding use of didanosine with **ZEFIN 300 mg TABLETS**
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

PREGNANCY AND LACTATION:
Safety and use in pregnancy and lactation has not been established. It is not known whether **ZEFIN 300 mg TABLETS** is excreted in human milk. (See "**CONTRAINDICATIONS**".)

DOSAGE AND DIRECTIONS FOR USE:
The dose of **ZEFIN 300 mg TABLETS** (tenofovir disoproxil fumarate) is 300 mg once daily taken orally, without regard to food.

Dose Adjustment for Renal Impairment:
Significantly increased exposure may occur when **ZEFIN 300 mg TABLETS** is administered to patients with moderate to severe renal impairment (See "**CONTRAINDICATIONS**").
The pharmacokinetics of **ZEFIN 300 mg TABLETS** have not been evaluated in non-haemodialysis patients with creatinine clearance < 10 mL/min; therefore, no dosing recommendation is available for these patients.

SIDE EFFECTS:
Gastrointestinal disorders:
Frequent:
Nausea, vomiting, diarrhoea
Less frequent:
Abdominal pain, flatulence, anorexia.
The following side effects have been reported and frequencies are unknown:
Pancreatitis, dyspepsia. Serum-amylase concentrations may be raised.

Neurological disorders:
The following side effects have been reported and frequencies are unknown:
Depression, headache, insomnia, peripheral neuropathy
Frequent: Dizziness.

Skin and subcutaneous tissue disorders:
The following side effects have been reported and frequencies are unknown: Skin rashes, sweating.

Musculoskeletal, connective tissue and bone disorders:
The following side effects have been reported and frequencies are unknown:
Myalgia and arthralgia. It is not known if long-term (more than 1 year) use of **ZEFIN 300 mg TABLETS** causes bone abnormalities. It is recommended that appropriate consultation be obtained if bone abnormalities are suspected.

Respiratory, thoracic and mediastinal disorders:
The following side effects have been reported and frequencies are unknown: Dyspnoea, pneumonia.

Blood and the lymphatic system disorders:
The following side effects have been reported and frequencies are unknown:
Neutropenia
Hepato-biliary disorders:
Less frequent:
Hepatotoxicity
The following side effects have been reported and frequencies are unknown:
Raised liver enzymes, hepatitis

Metabolism and nutrition disorders:
Less frequent:
Lactic acidosis, including fatal cases, usually associated with severe hepatomegaly and steatosis, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals.
The following side effects have been reported and frequencies are unknown:
Hypophosphataemia
Although a causal relationship has not been established, accumulation and redistribution of body fat, including breast enlargement, central obesity, cushingoid appearance, dorsocervical fat enlargement (buffalo hump), facial wasting, and peripheral wasting, have been seen in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these effects are not known.
Hypertriglyceridaemia
Hyperglycaemia

Renal and urinary disorders:
The following side effects have been reported and frequencies are unknown: Increased creatinine, proteinuria, nephrogenic diabetes insipidus, renal insufficiency, renal failure, acute renal failure, and effects on the renal proximal tubules, including Fanconi syndrome.

Immune system disorders:
The following side effect has been reported and frequency is unknown: Allergic reaction.

General disorders and administrative site conditions:
Frequent:
Asthenia
The following side effects have been reported and frequencies are unknown: Fever, weight loss, pain, back pain, chest pain.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate 300 mg is available. The effects of higher doses are not known. If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. **ZEFIN 300 mg TABLETS** is efficiently removed by haemodialysis with an extraction coefficient of approximately 54 %. Following a single 300 mg dose of **ZEFIN 300 mg TABLETS**, a four-hour haemodialysis session removed approximately 10 % of the administered tenofovir dose.

IDENTIFICATION:
White to off-white, oval shaped, biconvex, film-coated tablets debossed with 'I' on one side and '36' on the other side.

PRESENTATION:
HDPE Container Pack:
Tablets are packed in white opaque HDPE containers and white opaque closures with induction sealing wad with one no. of 1 g silica gel sachet and polyester fibre coil. Each container contains 30 tablets.
Pack size: 30's - One HDPE container contains 30 tablets.

STORAGE INSTRUCTIONS:
Store at or below 30 °C. Keep the containers tightly closed.
Do not use if seal over bottle opening is broken or missing.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
44/20.2.8/0307

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Novagen Pharma (Pty) Ltd.
Office 2, 100 Sovereign Drive
Route 21 Corporate Park
Nellmapius Drive
Irene – Pretoria
South Africa

DATE OF PUBLICATION OF THE PROFFESIONAL INFORMATION:
Date of registration: 30 April 2010
Date of latest revision of the text as approved by Council: 30 April 2010
Date of notification with regard to amended Reg. 9 and 10: 02 February 2015

↑ DETACH BEFORE DISPENSING

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
ZEFIN 300 mg TABLETS (Tablet)
Tenofovir disoproxil fumarate

Read all of this leaflet carefully before you start taking ZEFIN 300 mg TABLETS.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **ZEFIN 300 mg TABLETS** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT ZEFIN 300 mg TABLETS CONTAIN
The active substance is tenofovir disoproxil fumarate.
Each film-coated tablet contains 300 mg of tenofovir disoproxil fumarate.
The other ingredients are: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose and pregelatinized starch.
The coating ingredients contain: Hypromellose, lactose monohydrate, titanium dioxide (C.I. No: 77891), and triacetin.
Contains sugar: Lactose 120,83 mg.

2. WHAT ZEFIN 300 mg TABLETS ARE USED FOR
ZEFIN 300 mg TABLETS is a treatment for Human Immunodeficiency Virus (HIV) infection in adults. **ZEFIN 300 mg TABLETS** is always used in combination with other anti-HIV medicines to treat patients with HIV-1 infection.

3. BEFORE YOU TAKE ZEFIN 300 mg TABLETS
Do not take ZEFIN 300 mg TABLETS:
- If you are hypersensitive (allergic) to tenofovir disoproxil fumarate, or any of the other ingredients of **ZEFIN 300 mg TABLETS.**
- If you have kidney failure.
- If you are pregnant or breastfeeding.

Take special care with ZEFIN 300 mg TABLETS:

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

- **ZEFIN 300 mg TABLETS** 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. Patients who are very overweight are more at risk.
- If you became pregnant while taking **ZEFIN 300 mg TABLETS** your baby may develop blood and nervous system disorders. Your doctor will monitor your baby's condition.
- Pancreatitis is a dangerous inflammation of the pancreas that may cause death. Tell your doctor right away if you develop stomach pain, nausea or vomiting. These can be signs of pancreatitis.
- **ZEFIN 300 mg TABLETS** may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face and/or gain fat around the abdomen (tummy) and internal organs; get larger breasts or fatty lumps on the back of the neck (buffalo hump). The cause and the long-term effects of these changes are not yet known.
- If you are taking **ZEFIN 300 mg TABLETS** for the first time you may develop a condition known as Immune Reconstitution Inflammatory Syndrome (IRIS), within the first few months of treatment. This condition can cause opportunistic infections that are being treated to become worse or opportunistic diseases that were asymptomatic to be unmasked. Tell your doctor or healthcare professional if your general health worsens or if you think you may have an infection. You should not stop taking **ZEFIN 300 mg TABLETS.** Your doctor will treat the infections appropriately.
- Tell your doctor if you have liver disease (including hepatitis B). **ZEFIN 300 mg TABLETS** should not be used to treat chronic hepatitis B virus infection (HBV; an ongoing liver infection). Tell your doctor if you have or think you may have HBV.
- Tell your doctor if you have had kidney disease, or if tests have shown problems with your kidneys. **ZEFIN 300 mg TABLETS** may affect your kidneys.
- **ZEFIN 300 mg TABLETS** is not usually taken with other medicines that can damage your kidneys. If this is unavoidable, your doctor will monitor your kidney function.
- Inform your doctor or healthcare professional if you have any pre-existing liver disease including Hepatitis B or C.
- **ZEFIN 300 mg TABLETS** can have serious medicine interactions. Tell your doctor or healthcare professional about all other medicine you are taking (see **"Taking other medicines with ZEFIN 300 mg TABLETS").**
- You may develop a condition known as osteonecrosis while taking **ZEFIN 300 mg TABLETS**. Seek medical advice if you experience joint aches and pain, joint stiffness or difficulty in movement.
- Bone problems: Some patients taking combination antiretroviral therapy, including **ZEFIN 300 mg TABLETS** may develop a bone disease.
- You may continue to develop opportunistic infections and other complications of HIV infection while taking **ZEFIN 300 mg TABLETS.** You 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.
- You are still at risk of transmitting HIV to others through sexual contact or blood contamination while taking current antiretroviral therapy including **ZEFIN 300 mg TABLETS.** Appropriate precautions should continue to be employed.
- The safety and effectiveness of **ZEFIN 300 mg TABLETS** in children and patients younger than 18 years has not been determined.
- If you have advanced HIV infection (AIDS) and have any infection, you may develop acute symptoms of the infection or inflammation and a worsening of the symptoms of an existing infection once treatment with **ZEFIN 300 mg TABLETS** is started. If you notice signs of inflammation or infection, or deterioration thereof, tell your doctor at once.

Taking ZEFIN 300 mg TABLETS with food and drink:
ZEFIN 300 mg TABLETS can be taken with or without food.

Pregnancy and Breastfeeding:
- You must not take **ZEFIN 300 mg TABLETS** during pregnancy.
- Do not breastfeed during treatment with **ZEFIN 300 mg TABLETS**. It is not known whether the active substance in **ZEFIN 300 mg TABLETS** passes into human breast milk.

If you are pregnant or breastfeeding your baby please consult your doctor, pharmacist or other healthcare professional for advice before taking **ZEFIN 300 mg TABLETS**

Important information about some of the ingredients of ZEFIN 300 mg TABLETS
ZEFIN 300 mg TABLETS contains lactose (a type of sugar), if you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking **ZEFIN 300 mg TABLETS.**

Taking other medicines with ZEFIN 300 mg TABLETS:
Always tell your healthcare professional if you are taking any other medicine.
(This includes complementary or traditional medicines.)
- Tell your doctor if you are taking abacavir, emtricitabine, indinavir or lamivudine (for HIV infection).
- Tell your doctor if you are taking atazanavir and/or lopinavir/ ritonavir (for HIV infection): If you are taking any of these medicines, your doctor may need to monitor your therapy more closely or you may not be able to use **ZEFIN 300 mg TABLETS.**
- If you are taking **ZEFIN 300 mg TABLETS** and atazanavir together, you should also be taking ritonavir.
- Tell your doctor if you are taking other medicines containing didanosine (for HIV infection). Taking **ZEFIN 300 mg TABLETS** with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood. Inflammation of the pancreas, and neuropathy (disorders with the nerves) can occur. Your doctor will carefully consider whether to treat you with combinations of tenofovir and didanosine.
- 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.

4. HOW TO TAKE ZEFIN 300 mg TABLETS
Do not share medicines prescribed for you with any other person.
Always take **ZEFIN 300 mg TABLETS** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of **ZEFIN 300 mg TABLETS** is too strong or too weak, talk to your doctor or pharmacist.
Your doctor will tell you how long your treatment with **ZEFIN 300 mg TABLETS** will last.
- Stay under a healthcare provider's care when taking **ZEFIN 300 mg TABLETS.** Do not change your treatment or stop treatment without first talking with your healthcare provider.
- Always take **ZEFIN 300 mg TABLETS** in combination with other anti-HIV medicines.
- The usual dose of **ZEFIN 300 mg TABLETS** is one tablet once a day, taken with or without food.
- Tell your doctor if you have kidney problems.

If you take more ZEFIN 300 mg TABLETS than you should:
- Seek emergency medical attention if you think you have used too much of **ZEFIN 300 mg TABLETS.**

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

If you forget to take ZEFIN 300 mg TABLETS:
If you forget to take a dose, take it as soon as you remember, and then continue as before. Do not take a double dose to make up for forgotten individual doses.

5. POSSIBLE SIDE EFFECTS
ZEFIN 300 mg TABLETS can have side effects.
If any of the following happens, stop taking **ZEFIN 300 mg TABLETS** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Hives; difficulty breathing; swelling of your face, lips, tongue, or throat.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **ZEFIN 300 mg TABLETS**.You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
- Lactic acidosis (severe increase of lactic acid in the blood, a serious side effect that can be fatal) – The following side effects may be signs of lactic acidosis: deep rapid breathing, drowsiness, feeling sick (nausea), being sick (vomiting) and stomach pain.
- Liver damage – nausea; stomach pain; low fever; loss of appetite; dark urine; clay-coloured stools; jaundice (yellowing of the skin or eyes).
- Fever, chills, sore throat, cough, or other signs of infection.

These are all serious side effects. You may need urgent medical attention.
Tell your doctor if you notice any of the following side effects and they worry you or if any of these symptoms are severe or do not go away:
Headache; lack of energy; dizziness; sleep problems (inability to sleep); depression; problems with nerves; numbness, tingling, pins and needles; nausea (feeling sick); being sick (vomiting); diarrhoea; pain in the abdomen (tummy); heartburn; skin rashes, muscle pain; flatulence (excess amount of air/gas in stomach); lack of appetite; inflammation of the pancreas; inflammation of the liver; shortness of breath; pain; back pain; chest pain; kidney problems, fever; sweating; weight loss; changes in body fat, including an increased amount of fat in the upper back and neck, breast and around the trunk, loss of fat from the legs, arms and face may also happen.

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

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

6. STORING AND DISPOSING OF ZEFIN 300 mg TABLETS
Store at or below 30 °C (room temperature). Keep containers 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 ZEFIN 300 mg TABLETS
HDPE Container Pack:
Tablets are packed in white opaque HDPE containers and white opaque closures with induction sealing wad with one no. of 1 g silica gel sachet and polyester fibre coil. Each container contains 30 tablets. The HDPE container is further packed in a pre-printed carton with a packaging leaflet.
Pack size: 30's - One HDPE container contains 30 tablets.

8. IDENTIFICATION OF ZEFIN 300 mg TABLETS
White to off-white, oval shaped, biconvex, film-coated tablets debossed with 'I' on one side and '36' on the other side.

9. REGISTRATION NUMBER
44/20.2.8/0307

10. NAME AND ADDRESS OF REGISTRATION HOLDER
Novagen Pharma (Pty) Ltd.
Office 2, 100 Sovereign Drive
Route 21 Corporate Park
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(t) +27 (0)12 345 3175

11. DATE OF PUBLICATION
Date of registration: 30 April 2010
Date of latest revision of the text as approved by Council: 30 April 2010
Date of notification with regard to amended Reg. 9 and 10: 02 February 2015

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS:
S4

HANDELSNAAM EN DOSERINGSVORM:
ZEFIN 300 mg TABLETS (Tablet)

SAMESTELLING:
Elke filmbedekte tablet bevat 300 mg tenofovirdisoproksielfumaraat (wat gelykstaande is aan 245 mg tenofovirdisoproksiel).
Hulpmiddels: Natriumkroskarmellose, laktosemonohidraat, magnesiumstearaat, mikrokristallyne sellulose en pre-gelatineerde stysel.
Die deklagie Opadry II White bevat: Hipromellose, laktosemonohidraat, titaandioksied (Kleurindeksno.: 77891), en triasetien.
Bevat suiker: Laktose 120,83 mg.

WAARSKUWING:
MELKSUURASIDOSE EN ERGE HEPATOMEGALIE MET STEATOSE, WAARONDER STERFGEVALLE, IS MET DIE GEBRUIK VAN ZEFIN 300 mg TABLETS, ALLEEN OF IN KOMBINASIE MET ANDER ANTIRETROVIRALE MIDDELS, AANGEMELD (SIEN "WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS").
ZEFIN 300 mg TABLETS WORD NIE VIR DIE BEHANDELING VAN CHRONIESE HEPATITIS-B-VIRUS (HBV) AANGEDUI NIE EN DIE DOELTREFFENDHEID VAN ZEFIN 300 mg TABLETS IS NIE BY PASIËNTE WAT MET BEIDE HBV EN MIV BESMET IS, VASGESTEL NIE. ERNSTIGE AKUTE OPFLIKKERINGS VAN HEPATITIS-B IS AANGEMELD BY PASIËNTE WAT KO-INFEKSIE VAN HBV EN MIV HET EN WAT ZEFIN 300 mg TABLETS GESTAAK HET. LEWERFUNKSIE MOET NOUKEURIG GEMONITEER WORD, DEUR BEIDE KLINIESE EN LABORATORIUMOPVOLGING, VIR TEN MINSTE VERSKEIE MAANDE BY PASIËNTE WAT ZEFIN 300 mg TABLETS GESTAAK HET EN WAT 'n KO-INFEKSIE VAN MIV EN HBV HET. INDIEN TOEPASLIK, KAN INSTELLING VAN BEHANDELING VIR HEPATITIS-B GEREGVERDIG WEES (SIEN "WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS").

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

FARMAKOLOGIESE WERKING:
Werkingsmeganisme:
Tenofovirdisoproksielfumaraat is 'n asikliese nukleosiedfosfonaat diëster analoog van adenosienmonofosfaat. Tenofovirdisoproksielfumaraat benodig aanvanklike hidrolise van die diëster vir omskakeling na 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.

Medisyne-weerstand:
In vitro is MIV-1 isolate gekies met verminderde vatbaarheid vir tenofovir. Hierdie virusse het 'n K65R- mutasie in trutranskriptase uitgedruk en het 'n 2- tot 4-voudige verminderde vatbaarheid vir tenofovir getoon.
Tenofovir-weerstandige isolate van MIV-1 is ook by sommige pasiënte wat tenofovir in kombinasie met sekere antiretrovirale middels ontvang het, herwin. By behandeling-naïewe pasiënte wat met tenofovir + lamivudien + efavirens behandel is, het virale isolate van 8/47 (17 %) pasiënte met virologiese mislukking verminderde vatbaarheid vir tenofovir getoon. By behandelingservare pasiënte het 14/304 (4,6 %) van die pasiënte wat met tenofovir behandel is en wat virologiese mislukking deur week 96 getoon het, verminderde vatbaarheid vir tenofovir getoon. Genotipiese analise van die weerstandige isolate het 'n mutasie in die MIV-1 trutranskriptase geen getoon, wat tot die K65R aminosuur substitusie lei.

Kruisweerstandigheid:
Kruisweerstandigheid tussen sekere trutranskriptaseremmers is bekend. Die K65R-mutasie wat deur tenofovir geselekteer word, word ook by sommige pasiënte wat met MIV-1 besmet is en wat met abakavir, didanosien of salsitabien behandel word, geselekteer. MIV isolate met hierdie mutasie toon ook verminderde vatbaarheid vir emtrisitabien en lamivudien. Kruisweerstandigheid onder hierdie medisyne kan dus by pasiënte by wie die virus die K65R-mutasie huisves, voorkom. MIV-1 isolate van pasiënte (N = 20) by wie die MIV-1 gemiddeld 3 sidovudien-geassosieerde trutranskriptase mutasies uitgedruk het (M41L, D67N, K70R, L210W, T215Y/F of K219Q/E), het 'n 3,1-voudige afname in die vatbaarheid vir tenofovir getoon. MIV-1 met multinukleosied weerstandigheid met 'n T69S dubbelinvoeging mutasie in trutranskriptase toon verminderde vatbaarheid vir tenofovir.

Farmakodinamiese eienskappe:
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.
Die IC_{50} (50 % inhibitoriese konsentrasie) waardes vir tenofovir was binne die reikwydte van 0,04 – 8,5 µM. In geneesmiddel-kombinasie studies van tenofovir met nukleosied trutranskriptaseremmers (abakavir, didanosien, lamivudien, stavudien, salsitabien, sidovudien), nie-nukleosied trutranskriptaseremmers (delavirdien, efavirens, nevirapien) en proteaseremmers (amprenavir, indinavir, 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 (IC_{50} waardes het gereik van 0,5 – 2,2 µM). Die IC_{50} waardes van tenofovir teen MIV-2 het gereik van 1,6 µM tot 4,9 µM.

Farmakokinetiese eienskappe:
Die farmakokinetika van tenofovirdisoproksielfumaraat is by gesonde vrywilligers en MIV-1 besmette individue geëvalueer. Tenofovir se farmakokinetika stem ooreen tussen hierdie populasies.

Absorpsie:
Tenofovirdisoproksielfumaraat is 'n wateroplosbare diëster progeneesmiddel van die aktiewe bestanddeel, tenofovir. Die mondelike biobeskikbaarheid van tenofovirdisoproksielfumaraat is ongeveer 25 % by vastende pasiënte. Na orale toediening van 'n enkele dosis van tenofovir 300 mg aan MIV-1 besmette pasiënte in die vastende toestand, word maksimum serumkonsentrasies (K_{maks}) binne 1,0 ± 0,4 uur bereik. K_{maks} en AOK-waardes is onderskeidelik 296 ± 90 ng/ml en 2287 ± 685 ng*h/ml. Die farmakokinetika van tenofovir is proporsioneel met die dosis binne die dosis reikwydte van 75 tot 600 mg en dit word nie deur herhaalde dosisse beïnvloed nie.

Die effek van voedsel op orale absorpsie:
Toediening van tenofovir na 'n hoë-vet maaltyd (~ 700 tot 1 000 kkal met 40 tot 50 % vet) verhoog die orale biobeskikbaarheid, met 'n toename in tenofovir $AOK_{0-\infty}$ van ongeveer 40 % en 'n toename in K_{maks} van ongeveer 14 %. Toediening van tenofovir met 'n ligte ete het egter nie 'n beduidende uitwerking op die farmakokinetika van tenofovir gehad vergeleke met toediening van die medisyne in die vastende toestand was nie. Voedsel vertraag die tyd tot tenofovir K_{maks} met ongeveer 1 uur. K_{maks} en AOK van tenofovir is onderskeidelik 326 ± 119 ng/ml en 3 324 ± 1 370 ng*h/ml, na verskeie dosisse van tenofovir 300 mg een keer daagliks na maaltye, waarvan die inhoud nie gekontroleer was nie, gegee was.

Verspreiding:
In vitro is die binding van tenofovir aan mensplasma of serumproteïene onderskeidelik minder as 0,7 % en 7,2 %, oor die tenofovir-konsentrasiereeks van 0,01 tot 25 µg/ml. Na intraveneuse toediening van tenofovir 1,0 mg/kg en 3,0 mg/kg is die volume van verspreiding by ewewigstoestand 1,3 ± 0,6 l/kg en 1,2 ± 0,4 l/kg.

Metabolisme en uitskeiding:
In vitro studies dui daarop dat nóg tenofovirdisoproksiel, nóg tenofovir, substrate van CYP450 ensieme is. Na IV-toediening van tenofovir word ongeveer 70 - 80 % van die dosis binne 72 uur na dosering as onveranderde tenofovir in die urien herwin. Na 'n enkele orale dosis van tenofovir is die terminale eliminasiehalfleeftyd van tenofovir ongeveer 17 uur. Na veelvuldige orale dosisse van tenofovir 300 mg een keer daagliks (na maaltye), is 32 ± 10 % van die toegediende dosis na 24 uur in die urien herwin.

Tenofovir word deur 'n kombinasie van glomerulêre filtrasie en aktiewe tubulêre sekresie uitgeskei. Daar kan kompetisie met ander middels wees wat ook deur die niere uitgeskei word.

Spesiale populasies:
Die farmakokinetika van tenofovir is eenders by manlike en vroulike pasiënte. Farmakokinetiese studies is nie by kinders (< 18 jaar) of by bejaardes (> 65 jaar) gedoen nie.

Die farmakokinetiese eienskappe van tenofovir, na 'n enkeldosis van 300 mg, 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 in pasiënte met ingekorte lewerfunksie in vergelyking met pasiënte met normale lewerfunksie nie. Geen verandering in die dosis van tenofovir word vir pasiënte met swak lewerfunksie benodig nie.

Die farmakokinetika van tenofovir is anders by pasiënte met swak nierfunksie. By pasiënte met kreatinienopruiming <50 ml/min, of met eindstadium nierversaking (ESRD) wat dialise benodig, was die K_{maks} en $AOK_{0-\infty}$ van tenofovir verhoog. Dit word aanbeveel dat die doseringsinterval vir tenofovir gewysig word by pasiënte met kreatinienopruiming <50 ml/min, of by pasiënte met eindstadium-nierversaking (ESRD) wat hemodialise benodig (sien **"DOSERING EN GEBRUIKSAANWYSINGS"**).

Tenofovir word doeltreffend deur hemodialise verwyder, met 'n ekstraksiekoëffisiënt van ongeveer 54 %. Na 'n enkele 300 mg-dosis van tenofovir het 'n 4-uur hemodialisesessie ongeveer 10 % van die toegediende dosis van tenofovir verwyder.

INDIKASIES:
ZEFIN 300 mg TABLETS word in kombinasie met ander antiretrovirale middels vir die behandeling van MIV-1 infeksie aangedui.

KONTRAÏNDIKASIES:
ZEFIN 300 mg TABLETS is teenaangedui by:
- Pasiënte met voorheen bewese hipersensitiwiteit vir enige van die komponente van die produk.
- Matige tot ernstige nierversaking.
- Swangerskap en borsvoeding (sien **"SWANGERSKAP EN BORSVOEDING"**).

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS:
Daar is geen studieresultate wat die effek van **ZEFIN 300 mg TABLETS** op die kliniese progressie van MIV-1 aantoon nie.

Melksuurasidose/hiperlaktatemie/erge hepatomegalie met steatose:
Die gebruik van **ZEFIN 300 mg TABLETS** kan tot potensieel noodlottige laktasidose vanweë mitochondriese disfunksie lei.

Kliniese kenmerke is nie-spesifiek en sluit in naarheid, braking, buikpyn, dispnee, moegheid en gewigsverlies.
By pasiënte met verdagte simptome of biochemie word die veneuse laktaatvlak (normaal < 2 mmol/l) en serumbikarbonaat bepaal en dan soos volg opgetree:
Laktaat 2-5 mmol/l met min simptome: skakel oor na medisyne wat minder geneig is om melksuurasidose te veroorsaak.

Laktaat 5-10 mmol/l met simptome en/of met verminderde standaard bikarbonaat: - STAAK NRTIs en verander die behandelingsopsie. Sodra die laktaat gestabiliseer het, gebruik medisyne wat minder waarskynlik melksuurasidose sal veroorsaak. Sluit ander oorsake uit, (bv. sepsis, uremie, diabetiese ketoasidose, tirotoksikose en hipertiroïdisme).

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

Die bogenoemde laktaatwaardes kan moontlik nie van toepassing op pediatriese pasiënte wees nie.
Wees versigtig wanneer **ZEFIN 300 mg TABLETS** aan pasiënte met bekende risikofaktore vir lewersiekte toegedien word.
Behandeling met **ZEFIN 300 mg TABLETS** moet by enige pasiënt met kliniese of laboratorium bevindings wat dui op die ontwikkeling van melksuurasidose of hepatotoksisiteit, gestaak word.
Melksuurasidose en erge hepatomegalie met steatose, waaronder gevalle van sterftes, is aangemeld met die gebruik van nukleosied analoë soos **ZEFIN 300 mg TABLETS**, alleen of in kombinasie met ander antiretrovirale middels. Die meeste van hierdie gevalle was by vrouens gewees. Vetsug en verlengde nukleosiedblootstelling kan ook risikofaktore wees. Uiterste omsigtigheid is nodig wanneer nukleosied analoë, soos **ZEFIN 300 mg TABLETS**, aan enige pasiënt met bekende risikofaktore vir lewersiekte toegedien word; tog is komplikasies ook by pasiënte met geen bekende risikofaktore aangemeld. Behandeling met **ZEFIN 300 mg TABLETS** 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).

Mitochondriese disfunksie:
Nukleosied en nukleotied analoë soos **ZEFIN 300 mg TABLETS** 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 soos **ZEFIN 300 mg TABLETS** blootgestel was. Afgesien van melksuurasidose/hiperlaktatemie (sien hierbo), behels ander manifestasies van mitochondriese disfunksie hematologiese afwykings (anemie, neutropenie), en perifere neuropatie. Sommige neurologiese afwykings 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 in geval van relevante tekens of simptome, klinies en met laboratoriumtoetse opgevolg word en moet volledig ondersoek word vir moontlike mitochondriese disfunksie.

Pankreatitis:
Pankreatitis is by sommige pasiënte wat **ZEFIN 300 mg TABLETS** ontvang waargeneem. Pankreatitis moet oorweeg word wanneer 'n pasiënt buikpyn, naarheid, braking of verhoogde biochemiese merkers ontwikkel. Staak die gebruik van **ZEFIN 300 mg TABLETS** totdat 'n diagnose van pankreatitis uitgesluit kan word.

Lipodistrofie en metaboliese abnormaliteite:
Kombinasie- antiretrovirale behandeling is geassosieer met die herverspreiding/akkumulasie van liggaamsvet, waaronder sentrale obesiteit, dorso-servikale vet, vergroting (buffelnek), perifere uittering, uittering van die gesig, borsvergroting en verhoogde serum-lipiede en glukosekonsentrasies by MIV pasiënte. Kliniese ondersoek moet evaluering van fisiese tekens van 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 immuundisregulasie, wat kort na aanvang van kombinasie-antiretrovirale behandeling (kARB) voorkom. So 'n reaksie presenteer kenmerkend deur paradoksale agteruitgang van opportunistiese infeksies wat behandel word, of met ontmaskering van 'n asimptomatiese opportunistiese siekte, dikwels met 'n atipiese inflammatoriese presentasie. IRIS ontwikkel gewoonlik binne die eerste drie maande van aanvang van ARB en kom meer algemeen voor by pasiënte met lae CD4-tellings. Algemene voorbeelde van IRIS reaksies op opportunistiese siektes is tuberkulose, sitomegalovirus retinitis, en kriptokokmeningitis.

Geskikte behandeling van die opportunistiese siekte moet ingestel of voortgesit word en ARB 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 tuberkuleuse IRIS. Outo-immuunafwykings (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.

Pasiënte met matige tot erge ingekorte nierfunksie:
By pasiënte met matige tot ernstige swak nierfunksie is die terminale halfleeftyd van **ZEFIN 300 mg TABLETS** langer, as gevolg van verminderde opruiming. Die dosis van **ZEFIN 300 mg TABLETS** moet dus aangepas word (sien "**DOSERING EN GEBRUIKSAANWYSINGS**") Ingekorte nierfunksie, insluitende gevalle van akute nierversaking en Fanconi se sindroom (renale tubulêre skade met erge hipofosfatemie) is in assosiasie met die gebruik van **ZEFIN 300 mg TABLETS** aangemeld.

ZEFIN 300 mg TABLETS moet vermy word met gelyktydige of onlangse gebruik van 'n nefrotoksiese middel. Pasiënte met 'n risiko vir, of met 'n geskiedenis van nierdisfunksie, en pasiënte wat gelyktydig nefrotoksiese medisyne ontvang, moet noukeurig vir veranderinge in serumkreatinien en -fosfor gemoniteer word.

Lewersiekte:
Gebruik van **ZEFIN 300 mg TABLETS** kan lei tot hepatomegalie, vanweë nie-alkoholiese vetterige lewersiekte (hepatiese steatose). Die veiligheid en doeltreffendheid van **ZEFIN 300 mg TABLETS** is nog nie by pasiënte met belangrike onderliggende lewerafwykings/siektes bepaal nie. In die geval van gelyktydige antivirale behandeling vir hepatitis-B of C, raadpleeg asseblief ook die betrokke verpakkingsbiljette vir hierdie medisyne.

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

Pasiënte met MIV en hepatitis-B of -C virus ko-infeksie:
Dit word aanbeveel dat alle pasiënte met MIV vir die teenwoordigheid van hepatitis-B-virus (HBV) getoets moet word voordat antiretrovirale behandeling begin word. 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. **ZEFIN 300 mg TABLETS** word nie aangedui vir die behandeling van chroniese HBV-infeksie nie. Die veiligheid en doeltreffendheid van **ZEFIN 300 mg TABLETS** is nie by pasiënte wat terselfdertyd met HBV en MIV besmet is, vasgestel nie.

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

Pasiënte wat terselfdertyd met MIV en HBV besmet is en wat **ZEFIN 300 mg TABLETS** staak, moet nadat hulle behandeling met **ZEFIN 300 mg TABLETS** gestaak het, noulettend met kliniese waarneming en laboratoriumtoetse opgevolg word. By pasiënte met gevorderde lewersiekte of sirrose word staking van behandeling nie aanbeveel nie, aangesien opflikkering van hepatitis na die behandeling tot hepatiese dekompensasie kan lei.

Staking van behandeling met **ZEFIN 300 mg TABLETS** in pasiënte wat terselfdertyd met MIV en HBV besmet is, kan met ernstige, akute opflikkerings van hepatitis geassosieer word.
Indien toepaslik, kan die instelling van behandeling vir hepatitis-B geregverdig wees.

Geneesmiddelinteraksies (sien "INTERAKSIES"):
Die gelyktydige toediening van **ZEFIN 300 mg TABLETS** en didanosien as die gebufferde tablette of as die enteries-bedekte formulering, verhoog die K_{maks} en AOK van didanosien beduidend (sien Tabel 3). Die meganisme van die interaksie is onbekend. Hoër konsentrasies van didanosien kan didanosien-verwante newe-effekte potensieer, waaronder pankreatitis en neuropatie.
By volwassenes wat > 60 kg weeg moet die dosis van didanosien tot 250 mg verminder word as dit saam met **ZEFIN 300 mg TABLETS** toegedien word. Daar is geen inligting beskikbaar om 'n aanbeveling te kan maak oor aanpassing van die didanosien dosis by pasiënte wat < 60 kg weeg nie. Wanneer dit gelyktydig toegedien word, kan **ZEFIN 300 mg TABLETS** en didanosien onder vastende toestande, of met 'n ligte ete (<400 kkal, 20 % vet) geneem word. Gelyktydige toediening van didanosien gebufferde tablet formulering met **ZEFIN 300 mg TABLETS** moet onder vastende toestande geskied. **Gelyktydige toediening van ZEFIN 300 mg TABLETS 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.**
Dit is aangetoon dat atasanavir en lopinavir/ritonavir die konsentrasie van **ZEFIN 300 mg TABLETS** verhoog het. Die meganisme van die interaksie is onbekend. Pasiënte wat atasanavir en lopinavir/ritonavir en **ZEFIN 300 mg TABLETS** ontvang, moet gemoniteer word vir newe-effekte wat met **ZEFIN 300 mg TABLETS** geassosieer kan word. **ZEFIN 300 mg TABLETS** moet gestaak word by pasiënte wat newe-effekte ontwikkel wat met **ZEFIN 300 mg TABLETS** geassosieer kan word.
ZEFIN 300 mg TABLETS verminder die AOK en K_{min} van atasanavir. Wanneer dit saam met **ZEFIN 300 mg TABLETS** toegedien word, word dit aanbeveel dat atasanavir 300 mg ook saam met ritonavir 100 mg gegee word. Atasanavir moenie sonder ritonavir saam met **ZEFIN 300 mg TABLETS** toegedien word nie.

Aangesien **ZEFIN 300 mg TABLETS** hoofsaaklik deur die niere uitgeskei word, kan gesamentlike toediening van **ZEFIN 300 mg TABLETS** met medisyne wat die nierfunksie verminder, of wat vir aktiewe tubulêre sekresie kompeteer, die serumkonsentrasies van **ZEFIN 300 mg TABLETS** verhoog en/of die konsentrasies van ander medisyne wat deur die niere uitgeskei word, verhoog. 'n Paar voorbeelde sluit (onder andere) in adefovir dipivoksiel, sidofovir, asiklovir, valasiklovir, gansiklovir en valgansiklovir.

Hoër konsentrasies van **ZEFIN 300 mg TABLETS** kan **ZEFIN 300 mg TABLETS** geassosieerde newe-effekte, waaronder niersiektes, potensieer.

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

Effek op die been:
ZEFIN 300 mg TABLETS verminder beenmineraaldigtheid.
Been monitering moet oorweeg word vir MIV-geïnfekteerde pasiënte met 'n geskiedenis van patologiese beenfrakture, of wat 'n risiko vir osteopenie het. Hoewel die effek van aanvulling met kalsium en vitamien-D nie ondersoek is nie, kan hierdie aanvullings vir alle pasiënte voordelig wees. Indien beenafwykings vermoed word, moet geskikte konsultasie verkry word.

Opportunistiese infeksies:
Pasiënte wat **ZEFIN 300 mg TABLETS** 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 ervaring het van die behandeling van pasiënte met geassosieerde MIV-siekte, moet ontvang. Gereelde monitering van viruslading en CD4-tellings moet gedoen word.

Die risiko van MIV oordrag aan ander mense:
Pasiënte moet ingelig word dat huidige antiretrovirale behandeling, waaronder **ZEFIN 300 mg TABLETS**, nie die risiko van oordrag van MIV aan ander mense deur seksuele kontak of deur besmette bloed verhoed nie. Geskikte voorsorgmaatreëls moet voortdurend toegepas word.

Pediatriese gebruik:
Die veiligheid en doeltreffendheid vir pediatriese pasiënte < 18 jaar 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.

INTERAKSIES:
ZEFIN 300 mg TABLETS word hoofsaaklik deur die niere uitgeskei, deur 'n kombinasie van glomerulêre filtrasie en aktiewe tubulêre sekresie. Gelyktydige toediening van **ZEFIN 300 mg TABLETS** met medisyne wat deur aktiewe tubulêre sekresie uitgeskei word, kan serumkonsentrasies van óf **ZEFIN 300 mg TABLETS** óf die gelyktydige toegediende medisyne verhoog, as gevolg van kompetisie vir hierdie roete van eliminasie. Medisyne wat die nierfunksie verminder kan ook serumkonsentrasies van **ZEFIN 300 mg TABLETS** verhoog.
Tenofovir, soos bevat in **ZEFIN 300 mg TABLETS**, is ondersoek by gesonde vrywilligers in kombinasie met abakavir, adefovir dipivoksiel, atasanavir, didanosien, efavirens, emtrisitabien, indinavir, lamivudien, lopinavir/ritonavir, metadoon, orale voorbehoedmiddels en ribavirien. Tabelle 1 en 2 gee 'n oorsig van die farmakokinetiese effekte van gesamentlik toegediende medisyne op die farmakokinetika van **ZEFIN 300 mg TABLETS** en die effekte van **ZEFIN 300 mg TABLETS** op die farmakokinetika van ander medisyne wat gelyktydig geneem word.
Tabel 3 gee 'n oorsig van die geneesmiddelinteraksies tussen **ZEFIN 300 mg TABLETS** en didanosien. Wanneer 400 mg didanosien saam met verskeie dosisse van **ZEFIN 300 mg TABLETS** toegedien word, styg die K_{maks} en AOK van didanosien aansienlik. Die meganisme van die interaksie is onbekend. Wanneer didanosien 250 mg-enteries-bedekte kapsules saam met **ZEFIN 300 mg TABLETS** geneem word, is die sistemiese blootstelling aan didanosien soortgelyk aan dié wat met slegs die 400 mg enteries-bedekte kapsules onder vastende toestande waargeneem is.

Tabel 1: Geneesmiddelinteraksies: Verandering in farmakokinetiese parameters vir ZEFIN 300 mg tablette[1] in die teenwoordigheid van die gesamentlik toegediende medisyne.

Gesamentlik toegediende medisyne	Dosis van gesamentlik toegediende medisyne (mg)	N	% Verandering in ZEFIN 300 mg TABLETS se farmakokinetiese parameters[2] (90 % VI)		
			K_{maks}	AOK	K_{min}
Abakavir	300 een keer	8	<=>	<=>	NC
Adefovir dipivoksiel	10 een keer	22	<=>	<=>	<=>
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 (↑26 tot ↑38)	↑29 (↑32 tot ↑66)

1. Pasiënte het **ZEFIN 300 mg TABLETS** een keer daagliks ontvang
2. Toename = ↑; Afname = ↓; Geen effek = <=>; NC = Nie bereken nie

Na verskeie doserings aan MIV-negatiewe proefpersone wat chroniese instandhoudingsterapie met metadoon, óf orale voorbehoedmiddels, óf 'n enkele dosis van ribavirien ontvang het, 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 **ZEFIN 300 mg TABLETS**.

Tabel 2: Geneesmiddelinteraksies: Verandering in farmakokinetiese parameters van gesamentlik toegediende medisyne in die teenwoordigheid van ZEFIN 300 mg TABLETS.

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.
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	Lopinavir/Ritonavir 400/100 mg twee keer daagliks x 14 dae	21	<=>	<=>	<=>
Metadoon[2]	40-110 een keer daagliks x 14 dae[3]	13	<=>	<=>	<=>
Orale voorbehoedmiddels[4]	Etinielestradiol/Norgestimaat Een keer daagliks x 7 dae	20	<=>	<=>	<=>
Ribavirien	600 een keer	22	<=>	<=>	n.v.t.
Ritonavir	Lopinavir/Ritonavir 400/100 mg twee keer daagliks x 14 dae	24	<=>	<=>	<=>
Atasanavir	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 mg een keer daagliks x 42 dae	10	↓28 (↓50 tot ↑5)	↓25 (↓42 tot ↓3)	↓23[5] (↓46 tot ↑10)

1. Toename = ↑; Afname = ↓; Geen effek = <=>; n.v.t. = nie van toepassing nie
2. R- (aktiewe), S-en totale metadoon blootstelling het ooreengestem, hetsy dit alleen, of saam met **ZEFIN 300 mg TABLETS**, gedoseer was.
3. Individuele proefpersone was op hulle gestabiliseerde dosis van metadoon onderhou. Daar was geen farmakodinamiese veranderings (opiaat-toksisiteit en tekens of simptome van onttrekking) aangemeld nie.
4. Etinielestradiol en 17-deasetiel norgestimaat (farmakologies aktiewe metaboliet) se blootstelling was dieselfde, hetsy dit alleen, of saam met **ZEFIN 300 mg TABLETS** gedoseer was.
5. By MIV-besmette pasiënte het die toevoeging van tenofovir DF 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.

Tabel 3: Geneesmiddelinteraksies: Farmakokinetiese parameters vir didanosien in die teenwoordigheid van ZEFIN 300 mg TABLETS.

Didanosien[1] dosis mg/Metode van toediening[2]	ZEFIN 300 mg TABLETS 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 "VOORSORGMAATREËLS" vir die gebruik van of didanosien met **ZEFIN 300 mg TABLETS**
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 ddI 250 mg ontvang het.

SWANGERSKAP EN BORSVOEDING:
Die veiligheid van gebruik tydens swangerskap en borsvoeding is nie bepaal nie. Dit is nie bekend of **ZEFIN 300 mg TABLETS** in borsmelk uitgeskei word nie. (Sien **"KONTRAÏNDIKASIES"**).

DOSERING EN GEBRUIKSAANWYSINGS:
Die dosis van **ZEFIN 300 mg TABLETS** (tenofovirdisoproksielfumaraat) is 300 mg een keer daagliks, oraal geneem, met of sonder voedsel.

Aanpassing van die dosis vir swak nierfunksie:
'n Aansienlike toename in blootstelling aan die medisyne het voorgekom nadat **ZEFIN 300 mg TABLETS** aan pasiënte met matig tot erg verswakte nierfunksie toegedien is (sien **"KONTRAÏNDIKASIES"**).
Die farmakokinetika van **ZEFIN 300 mg TABLETS** is nie by nie-hemodialise pasiënte met kreatinienopruiming < 10 ml/min geëvalueer nie; dus kan geen aanbeveling vir die dosis by hierdie pasiënte gemaak word nie.

NEWE-EFFEKTE:
Gastroïntestinale afwykings:
Dikwels:
Naarheid, braking, diarree
Minder dikwels:
Buikpyn, winderigheid, anoreksie.
Die volgende newe-effekte is aangemeld maar die frekwensie is onbekend:
Pankreatitis, dispepsie. Serum-amilase konsentrasies kan verhoog wees.

Neurologiese afwykings:
Die volgende newe-effekte is aangemeld maar die frekwensie is onbekend:
Depressie, hoofpyn, slapeloosheid, perifere neuropatie
Dikwels: Duiseligheid.

Vel- en onderhuidse weefselafwykings:
Die volgende newe-effekte is aangemeld maar die voorkoms is onbekend: Veluitslag, sweet.

Muskuloskeletale-, bindweefsel en beenafwykings:
Die volgende newe-effekte is aangemeld maar die frekwensie is onbekend:
Mialgie en artralgie. Dit is nie bekend of langtermyn (meer as 1 jaar) gebruik van **ZEFIN 300 mg TABLETS** beenabnormaliteite veroorsaak nie. Dit word aanbeveel dat paslike konsultasie verkry word indien beenabnormaliteite vermoed word.

Respiratoriese-, bors en mediastinale afwykings:
Die volgende newe-effekte is aangemeld, maar die frekwensie is onbekend: Dispnee, pneumonie.

Bloed- en limfstelselafwykings:
Die volgende newe-effekte is aangemeld maar die frekwensie is onbekend:
Neutropenie

Hepatobiliêre afwykings:
Minder dikwels:
Hepatotoksisiteit
Die volgende newe-effekte is aangemeld maar die frekwensie is onbekend:
Verhoogde lewerensieme, hepatitis

Metabolisme en voedingsafwykings:
Minder dikwels:
Melksuurasidose, waaronder gevalle van sterftes, gewoonlik geassosieer met erge hepatomegalie met steatose, is met die gebruik van nukleosied analoë, alleen of in kombinasie met antiretrovirale middels, aangemeld.
Die volgende newe-effekte is aangemeld maar die frekwensie is onbekend:
Hipofosfatemie
Alhoewel 'n oorsaaklike verband nie vasgestel is nie, is opeenhoping en herverdeling van liggaamsvet, insluitend vergrote borste, sentrale vetsug, Cushing-agtige voorkoms, vergroting van dorsoservikale vet (buffelnek), uitgeteerde gesig en perifere uittering waargeneem by pasiënte wat antiretrovirale terapie ontvang. Die meganisme en langtermyn gevolge van hierdie effekte is nie bekend nie.
Hipertrigliseridemie
Hiperglukemie

Nier- en urienwegafwykings:
Die volgende newe-effekte is aangemeld en die frekwensie is onbekend: Verhoogde kreatinien, proteïenurie, nefrogene diabetes insipidus, swak nierfunksie, nierversaking, interstisiële nefritis, akute nierversaking, en effekte op die proksimale nierkronkelbuisies, waaronder Fanconi se sindroom.

Immuunstelselafwykings:
Die volgende newe-effek is aangemeld maar die frekwensie daarvan is onbekend: Allergiese reaksie.

Algemene afwykings en toestande by die plek van toediening:
Dikwels:
Astenie
Die volgende newe-effekte is aangemeld maar die frekwensie is onbekend: Koors, gewigsverlies, pyn, rugpyn, borspyn.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:
Daar is beperkte kliniese ondervinding by dosisse wat hoër is as die terapeutiese dosis van 300 mg tenofovirdisoproksielfumaraat. Die effekte van hoër dosisse is nie bekend nie. Indien oordosering voorkom moet die pasiënt vir tekens van toksisiteit gemoniteer word en standaard ondersteunende behandeling moet soos nodig toegepas word. **ZEFIN 300 mg TABLETS** word doeltreffend deur hemodialise verwyder, met 'n ekstraksiekoëffisiënt van ongeveer 54 %. Na 'n enkele 300 mg-dosis van **ZEFIN 300 mg TABLETS** het 'n 4-uur hemodialisesessie ongeveer 10 % van die toegediende dosis van tenofovir verwyder.

IDENTIFIKASIE:
Wit tot naaswit ovaalvormige, bikonvekse filmbedekte tablette, gebosseleer met "I" op die een kant en "36" aan die ander kant.

AANBIEDING:
HDPE verpakking:
Tablette verpak in wit ondeursigtige HDPE houers en wit ondeursigtige induksie-verseëlde prop met 'n no. 1 g kieseljelsakkie en poliësterveselspoel. Elke houer bevat 30 tablette.

Verpakking: 30's - Een HDPE-houer bevattende 30 tablette.

BERGINGSAANWYSINGS:
Bewaar by of benede 30 °C. Hou die houer diggeslote.
Moenie gebruik as die seël wat die houer bedek gebreek is, of nie teenwoordig is nie.

HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:
44/20.2.8/0307

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT:
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DATUM VAN PUBLIKASIE VAN DIE PROFESSIONELE INLIGTING
Datum van registrasie: 30 April 2010
Datum van laaste hersiening van die teks soos goedgekeur deur die raad: 30 April 2010
Datum van kennisgewing aangaande gewysigde Reg. 9 en 10: 02 Februarie 2015

P1526405

DETACH BEFORE DISPENSING

PASIËNTINLIGTINGSBILJET

SKEDULERINGSTATUS
S4

HANDELSNAAM, STERKTE EN FARMASEUTIESE VORM
ZEFIN 300 mg TABLETS (Tablet)
Tenofovirdisoproksielfumaraat

Lees die hele pamflet deeglik deur voordat jy begin om ZEFIN 300 mg TABLETS te gebruik.
- Hou hierdie pamflet. Dit is moontlik dat jy dit weer sal wil deurlees.
- Indien jy nog vrae het, raadpleeg asseblief jou dokter of apteker.
- **ZEFIN 300 mg TABLETS** is vir jou persoonlik voorgeskryf en jy moenie jou medisyne met ander mense deel nie. Dit kan skadelik vir hulle wees, selfs al is hulle simptome dieselfde as joune.

1. WAT ZEFIN 300 mg TABLETS BEVAT
Die aktiewe bestanddeel is tenofovirdisoproksielfumaraat.
Elke filmbedekte tablet bevat 300 mg tenofovirdisoproksielfumaraat.
Die ander bestanddele is: Natriumkroskarmellose, laktosemonohidraat, magnesiumstearaat, mikrokristallyne sellulose en pre-gelatineerde stysel.
Die deklagie bevat: Hipromellose, laktosemonohidraat, titaandioksied (Kleurindeksno.: 77891), en triasetien.
Bevat suiker: Laktose 120,83 mg.

2. WAARVOOR ZEFIN 300 mg TABLETS GEBRUIK WORD
ZEFIN 300 mg TABLETS is 'n behandeling vir Mens-Immuungebrekvirus (MIV) by volwassenes. **ZEFIN 300 mg TABLETS** word altyd in kombinasie met ander anti-MIV-medisyne gebruik om pasiënte met MIV-1 infeksie te behandel.

3. VOORDAT JY ZEFIN 300 mg TABLETS NEEM
Moenie ZEFIN 300 mg TABLETS neem nie:
- As jy hipersensitief (allergies) is vir tenofovirdisoproksielfumaraat, of vir enige van die ander bestanddele van **ZEFIN 300 mg TABLETS** nie.
- Indien jy nierversaking het.
- Indien jy swanger is, of borsvoed.

Wees veral versigtig met ZEFIN 300 mg TABLETS:

ZEFIN 300 mg TABLETS kan 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 ZEFIN 300 mg TABLETS is nie by pasiënte wat met beide die mens-immuungebrekvirus (MIV) en hepatitis-B-virus (HBV) besmet is, vasgestel nie. ZEFIN 300 mg TABLETS moenie 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 HBV-infeksie het en jy hou op om ZEFIN 300 mg TABLETS te neem.

- **ZEFIN 300 mg TABLETS** kan melksuurasidose veroorsaak, wat saam 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 voor by vrouens. Pasiënte wat baie oorgewig is, is aan 'n groter risiko onderworpe.
- As jy swanger raak terwyl jy **ZEFIN 300 mg TABLETS** neem, kan jou baba bloed- en senuweestelselsfwykings ontwikkel. Jou dokter sal jou baba se toestand moniteer.
- Pankreatitis is 'n gevaarlike ontsteking van die pankreas, wat dood kan veroorsaak. Lig jou dokter dadelik in as jy maagpyn, naarheid of braking ontwikkel. Dit kan tekens van pankreatitis wees.
- **ZEFIN 300 mg TABLETS** kan jou liggaamsvorm verander, deur die manier waarop die liggaamsvet versprei word, te verander. Jy kan vet aan jou bene, arms en gesig verloor; en/of vet aanpak om die maag en inwendige organe; groter borste kry of 'n vetkussing agter op die nek (buffelskof). Die oorsaak en langtermyn effek van hierdie veranderinge is nog nie bekend nie.
- As jy **ZEFIN 300 mg TABLETS** vir die eerste keer neem, kan jy binne die eerste paar maande van behandeling 'n toestand bekend as Immuunrestourasie Inflammatoriese Sindroom (IRIS) ontwikkel. Hierdie siektetoestand kan opportunistiese infeksies wat behandel word laat erger word, of opportunistiese siektes wat asimptomaties was, ontmasker. Lig jou dokter of gesondheidsorgkundige in as jou algemene gesondheid versleg, of as jy dink dat jy 'n infeksie het. Jy moenie ophou om **ZEFIN 300 mg TABLETS** te neem nie. Jou dokter sal die infeksies op geskikte wyse behandel.
- Lig jou dokter in as jy 'n lewersiekte het (waaronder hepatitis-B). **ZEFIN 300 mg TABLETS** moenie gebruik word om chroniese hepatitis-B-virus infeksie (HBV; 'n voortslepende lewerinfeksie) te behandel nie. Lig jou dokter in as HBV het, of dink dat jy dit kan hê.
- Lig jou dokter in jy niersiekte het, of as toetse wys dat jy nier-probleme het. **ZEFIN 300 mg TABLETS** kan jou niere aantas.
- **ZEFIN 300 mg TABLETS** word gewoonlik nie saam met ander medisyne geneem wat jou niere kan beskadig nie. Indien dit onvermydelik is, sal jou dokter jou nierfunksie dophou.
- Lig jou dokter of gesondheidsorgkundige in as jy enige voorafbestaande lewersiekte, waaronder hepatitis-B of -C het.
- **ZEFIN 300 mg TABLETS** kan ernstige geneesmiddelinteraksies veroorsaak. Lig jou dokter of gesondheidsorgkundige in van alle ander medisyne wat jy neem (sien **"Neem van ander medisyne met ZEFIN 300 mg TABLETS")**.
- Jy kan 'n siektetoestand bekend as osteonekrose ontwikkel terwyl jy **ZEFIN 300 mg TABLETS** neem. Kry mediese raad indien jy pyne in die gewrigte, gewrigstyfheid of probleme met beweging ervaar.
- Beenprobleme: Sommige pasiënte wat kombinasie antiretrovirale behandeling, insluitend **ZEFIN 300 mg TABLETS** kry, kan 'n beensiekte ontwikkel.
- Jy kan steeds opportunistiese infeksies en ander komplikasies van MIV-infeksie ontwikkel, terwyl jy **ZEFIN 300 mg TABLETS** neem. Jy moet heeltyd onder noukeurige waarneming bly van gesondheidsorgkundiges wat ervare is in die behandeling van pasiënte met MIV-geassosieerde siektes. Gereelde monitering van viruslading en CD4-tellings moet gedoen word.
- Daar is steeds 'n risiko dat jy terwyl jy antiretrovirale behandeling ontvang, waaronder **ZEFIN 300 mg TABLETS**, MIV aan ander mense deur seksuele kontak of besmetting met bloed kan oordra. Geskikte voorsorgmaatreëls moet voortdurend toegepas word.
- Die veiligheid en doeltreffendheid van **ZEFIN 300 mg TABLETS** by kinders en pasiënte jonger as 18 jaar is nie bepaal nie.
- Indien jy gevorderde MIV-infeksie (VIGS) het en 'n infeksie opdoen, kan jy akute simptome van die infeksie of ontsteking, of erger simptome van 'n bestaande infeksie ontwikkel, sodra behandeling met **ZEFIN 300 mg TABLETS** begin word. Indien jy tekens van ontsteking of infeksie opmerk en jou toestand versleg, sê dadelik vir jou dokter daarvan.

Neem van ZEFIN 300 mg TABLETS saam met kos en vloeistof:
ZEFIN 300 mg TABLETS kan met of sonder kos geneem word.

Swangerskap en borsvoeding:
- Jy moenie **ZEFIN 300 mg TABLETS** tydens swangerskap neem nie.
- Moenie borsvoed tydens behandeling met **ZEFIN 300 mg TABLETS** nie. Dit is nie bekend of die aktiewe bestanddeel in **ZEFIN 300 mg TABLETS** in die borsmelk uitgeskei word nie.

Indien jy swanger is, of jou baba borsvoed, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgkundige voordat jy **ZEFIN 300 mg TABLETS** neem.

Belangrike inligting oor sommige van die bestanddele van ZEFIN 300 mg TABLETS
ZEFIN 300 mg TABLETS bevat laktose ('n tipe suiker). Indien u ingelig is deur u dokter dat u 'n onverdraagsaamheid teenoor sommige suikers het, kontak u dokter voordat u **ZEFIN 300 mg TABLETS** neem.

Neem van ander medisyne saam met ZEFIN 300 mg TABLETS:
Lig altyd jou gesondheidsorgkundige in as jy enige ander medisyne neem.

(Dit sluit komplementêre of tradisionele medisyne in.)
- Lig jou dokter in as jy abakavir, emtrisitabien, indinavir of lamivudien (vir MIV-infeksie) neem.
- Lig jou dokter in as jy atasanavir en/of lopinavir/ritonavir (vir MIV-infeksie) neem: As jy enige van hierdie medisyne neem, sal jou dokter jou behandeling meer noukeurig wil dophou en dit is moontlik dat jy nie **ZEFIN 300 mg TABLETS** as behandeling sal kan gebruik nie.
- As jy **ZEFIN 300 mg TABLETS** en atasanavir gelyktydig neem, moet jy ook ritonavir neem.
- Lig jou dokter in as jy enige medisyne neem wat didanosien (vir MIV-infeksie) bevat. As jy **ZEFIN 300 mg TABLETS** saam met ander antivirale medisyne neem wat didanosien bevat, kan dit die konsentrasie van didanosien in jou bloed verhoog. Ontsteking van die pankreas en neuropatie (senuwee-aantasting) kan voorkom. Jou dokter sal sorgvuldig oorweeg of jy behandel kan word met kombinasies van tenofovir en didanosien
- Lig jou dokter in as jy enige ander medisyne neem wat jou nierfunksie kan verswak. 'n Paar voorbeelde sluit in, maar word nie beperk tot adefovirdipivoksiel, sidofovir, asiklovir, valasiklovir, gansiklovir en valgansiklovir nie.

4. HOE OM ZEFIN 300 mg TABLETS TE NEEM
Moenie medisyne wat vir jou voorgeskryf is met 'n ander persoon deel nie.

Neem **ZEFIN 300 mg TABLETS** 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 **ZEFIN 300 mg TABLETS** te sterk of te swak is, lig jou dokter of apteker in.
Jou dokter sal jou inlig hoe lank jou behandeling met **ZEFIN 300 mg TABLETS** sal aanhou.
- Bly onder die sorg van 'n gesondheidsorgkundige as jy **ZEFIN 300 mg TABLETS** neem. Moenie jou behandeling verander of jou behandeling staak sonder om eers met jou gesondheidsorgkundige te praat nie.
- Neem altyd **ZEFIN 300 mg TABLETS** in kombinasie met ander anti-MIV-medisyne.
- Die gewone dosis van **ZEFIN 300 mg TABLETS** is een tablet een keer daagliks, met of sonder kos geneem.
- Lig jou dokter in as jy nierprobleme het.

Indien jy meer ZEFIN 300 mg TABLETS geneem het as wat jy moes:
- Kry nood-mediese hulp as jy dink dat jy te veel **ZEFIN 300 mg TABLETS** geneem het.

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

Indien jy vergeet om ZEFIN 300 mg TABLETS te neem:
As jy vergeet het om 'n dosis te neem, neem dit sodra jy daarvan onthou en gaan dan aan soos voorheen. Moenie 'n dubbele dosis neem om op te maak vir vergete individuele dosisse nie.

5. MOONTLIKE NEWE-EFFEKTE
ZEFIN 300 mg TABLETS kan newe-effekte hê.
Indien enige van die volgende gebeur, staak **ZEFIN 300 mg TABLETS** en lig dadelik jou dokter daarvan in, of gaan na die ongevalle-afdeling by jou naaste hospitaal:
- Netelroos (galbulte); moeilike asemhaling; geswelde gesig, lippe, tong of keel.

Hierdie is almal baie ernstige newe-effekte. Indien jy dit ervaar, kan jy moontlik 'n ernstige allergiese reaksie op **ZEFIN 300 mg TABLETS** 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:
- Melksuurasidose (ernstige toename van melksuur in die bloed, 'n ernstige newe-effek wat dodelik kan wees). Die volgende newe-effekte kan tekens van melksuurasidose wees: diep vinnige asemhaling, lomerigheid, naarheid, braking en maagpyn .
- Lewerskade - naarheid; maagpyn; lae koors; swak eetlus, donker urine; stoelgange met die kleur van klei; geelsug (geel verkleuring van die vel of oë).
- Koors, koue rillings, seer keel, hoes, of ander tekens van infeksie.

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

Lig jou dokter in as jy enige van die volgende newe-effekte waarneem en hulle bekommer jou, of as enige van die simptome ernstig is en nie opklaar nie:

Hoofpyn; 'n gebrek aan energie; duiseligheid, slaapprobleme (onvermoë om te slaap); depressie; senuweeprobleme; gevoelloosheid, tinteling, naalde-en-spelde; naarheid; braking; diarree; pyn in die buik (maag); sooibrand; veluitslag, spierpyn, winderigheid (oortollige hoeveelheid lug/gas in die maag); 'n swak eetlus; ontsteking van die pankreas; ontsteking van die lewer; kortasem; pyn; rugpyn; borspyn; nierprobleme, koors, sweet; gewigsverlies; veranderinge in die liggaamsvet, insluitend 'n verhoogde hoeveelheid vet in die bo-rug en nek, bors en rondom die liggaam, verlies van vet van die bene, arms en gesig kan ook voorkom.

Nie alle newe-effekte wat vir **ZEFIN 300 mg TABLETS** aangemeld is, is by hierdie inligtingsbiljet ingesluit nie. Indien jou algemene gesondheid agteruitgaan of jy enige ongunstige effekte ervaar terwyl jy **ZEFIN 300 mg TABLETS** neem, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgkundige.

Indien jy enige newe-effekte waarneem wat nie in hierdie pamflet vermeld word nie, lig jou dokter of apteker in.

6. BERGING EN WEGDOENING VAN ZEFIN 300 mg TABLETS
Bêre by, of benede 30 °C (kamertemperatuur)**.** Sorg dat die houers dig toe bly.
Moenie gebruik as die seël wat die houer bedek gebreek is, of nie teenwoordig is nie.
Berg 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 ZEFIN 300 mg TABLETS
HDPE Verpakking:
Tablette word verpak in wit ondeursigtige HDPE houers met wit ondeursigtige sluitings met 'n induksie-seëlingprop met een 1 g silikagelsakkie en poliësterveselspoel. Elke houer bevat 30 tablette. Die HDPE houer word verder verpak in 'n voorafgedrukte karton met 'n verpakkingsbiljet.
Pakgrootte: 30's - Een HDPE-houer bevat 30 tablette.

8. IDENTIFIKASIE VAN ZEFIN 300 mg TABLETS
Wit tot naaswit, ovaalvormige, bikonvekse filmbedekte tablette, gebosseleer met "I" op die een kant en "36" aan die ander kant.

9. REGISTRASIENOMMER
44/20.2.8/0307

10. NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:
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11. DATUM VAN PUBLIKASIE
Datum van registrasie: 30 April 2010
Datum van laaste hersiening van die teks soos goedgekeur deur die raad: 30 April 2010
Datum van kennisgewing aangaande gewysigde Reg. 9 en 10: 02 Februarie 2015