ERIGE CAPSULES
P1522657

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P1522657

NOVAGEN® Pharma

PROFESSIONAL INFORMATION

SCHEDULING STATUS
SOUTH AFRICA: S4

PROPRIETARY NAME AND DOSAGE FORM
ERIGE 50 mg CAPSULES (Capsule)
ERIGE 100 mg CAPSULES (Capsule)
ERIGE 200 mg CAPSULES (Capsule)

COMPOSITION
ERIGE 50 mg CAPSULES:
Each capsule contains 50 mg efavirenz.
ERIGE 100 mg CAPSULES:
Each capsule contains 100 mg efavirenz.
ERIGE 200 mg CAPSULES:
Each capsule contains 200 mg efavirenz.
Excipients: Lactose monohydrate, magnesium stearate, sodium starch glycolate and sodium lauryl sulfate.
Contains sugar (lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION
A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Mechanism of action:
Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type I HIV-1. Efavirenz diffuses into the cell where it binds adjacent to the active site of reverse transcriptase. This produces a conformational change in the enzyme and inhibits its function. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) with respect to template, primer or nucleoside triphosphates, with a small component of competitive inhibition. HIV-2 RT and human cellular DNA polymerases alpha, beta, gamma and delta are not inhibited by concentrations of efavirenz.

***In vitro* HIV susceptibility:**
The clinical significance of *in vitro* susceptibility of HIV-1 to efavirenz has not been established. The *in vitro* antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The 90 to 95 % inhibitor concentration (IC_{90-95}) of efavirenz for wild type laboratory adapted strains and clinical isolates ranged from 1,7 to 25 nM. Efavirenz demonstrated synergistic activity in cell culture in combination with the nucleoside analogue reverse transcriptase inhibitors (NRTIs), zidovudine (ZDV) or didanosine (ddi), or the protease inhibitor, indinavir (IDV).
In vitro sensitivity does not necessarily imply clinical sensitivity.

Resistance:
HIV-1 isolates with reduced susceptibility to efavirenz (greater than 380-fold increase in IC_{90}) compared to baseline can emerge *in vitro*. Phenotypic changes in evaluable HIV-1 isolates and genotypic changes in plasma virus from selected patients treated with efavirenz in combination with IDV or with ZDV plus lamivudine were monitored. One or more RT mutations at amino acid positions 100, 101, 103, 108, 190 and 225, were observed in all 62 patients with a frequency of at least 10 % compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagines) was the most frequently observed (greater or equal to 90 %). A mean loss in susceptibility (IC_{90}) to efavirenz of 47-fold was observed in 26 clinical isolates. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9 to greater than 312-fold increase in IC_{90}) were observed for these isolates *in vitro* compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with efavirenz therapy has not been established.

Cross-resistance:
Rapid emergence of HIV-1 strains that are cross-resistant to non-nucleoside RT inhibitors has been observed *in vitro*. Clinical isolates previously characterized as efavirenz-resistant were also phenotypically resistant to nevirapine and delavirdine *in vitro* compared to baseline. Clinically derived ZDV-resistant HIV-1 isolated and tested *in vitro* retained susceptibility to efavirenz. Cross-resistance between efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

Pharmacokinetic properties
Absorption: Peak efavirenz plasma concentrations of 1,6 - 9,1 μM were attained by 5 hours following single oral doses of 100 mg to 1 600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1 600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Steady state plasma concentrations are reached in 6 -7 days.

Distribution: Efavirenz is very highly bound (approximately 99,5 – 99,75 %) to human plasma proteins, predominantly albumin. In HIV-1 infected patients who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0,26 to 1,19 % (mean 0,69 %) of the corresponding plasma concentration. This proportion is approximately three-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism: Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are inactive against HIV-1. CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism.

Elimination: Efavirenz has a long terminal half-life of 52 to 76 hours after single doses, and 40 - 55 hours after multiple doses. Approximately 14 - 34 % of a radio-labelled dose of efavirenz was recovered in the urine and 16 - 61 % was recovered in faeces, mainly in the form of metabolites.

Special populations:

Hepatic impairment:
The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment.

Renal impairment:
The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency. However, less than 1 % of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Gender and Race:
Pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

Geriatric use:
Pharmacokinetics of efavirenz have not been studied in subjects aged 65 and over to establish whether they respond differently.

Paediatric use:
In 49 paediatric patients receiving the equivalent of a 600 mg dose of efavirenz (dose adjusted from calculated body size based on weight), steady state C_{max} was 14.2 μM, steady state C_{min} was 5,6 μM, and AUC was 218 μM. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

INDICATIONS
ERIGE CAPSULES, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infected adults, adolescents and children weighing 40 kg and above, and/or 3 years and above.

CONTRAINDICATIONS
ERIGE CAPSULES is contraindicated in patients with hypersensitivity to **ERIGE CAPSULES** or any of it components.
ERIGE CAPSULES should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events [e.g. cardiac arrhythmias, prolonged sedation or respiratory depression].
Pregnancy and lactation (see "**PREGNANCY AND LACTATION**"). Children less than 3 years or weighing less than 40 kg.

WARNINGS and SPECIAL PRECAUTIONS
ALERT: Find out about medicines that should NOT be taken with ERIGE CAPSULES (see **"CONTRAINDICATIONS"** and **"SIDE EFFECTS").**
Resistant virus emerges rapidly when **ERIGE CAPSULES** is administered as monotherapy, therefore**, ERIGE CAPSULES** must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen.Serious nervous system and psychiatric symptoms have been reported.
When prescribing medications concomitantly with **ERIGE CAPSULES**, medical practitioners should refer to the corresponding manufacturer's product circular. If any antiretroviral medication in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medications. The antiretroviral medications should be restarted at the same time upon resolution of the intolerance symptoms. Intermittent monotherapy and sequential reintroduction of antiretroviral agents is not advisable because of the increased potential for selection of drug-resistant mutant virus.

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.

Skin Rash:
Mild to-moderate rash has been reported with **ERIGE CAPSULES** use and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. **ERIGE CAPSULES** should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with **ERIGE CAPSULES** is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of drug resistant virus (see "**Side Effects**").
Prophylaxis with appropriate antihistamines prior to initiating therapy with **ERIGE CAPSULES** in children may be considered.

Immune Reconstitution Inflammatory Syndrome:
Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are 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.

Nervous System Symptoms:
Nervous system symptoms have been reported with **ERIGE CAPSULES** use (see "**Side Effects**"). In addition, there have been reports of psychosis-like reactions, such as delusions and inappropriate behaviour (including aggressive reactions), predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both **ERIGE CAPSULES** -treated and control-treated patients, particularly in patients with a previous history of depression. Patients should be advised that if they experience these symptoms they should contact their doctor immediately because discontinuation of **ERIGE CAPSULES** may be required.

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

Opportunistic infections:
Patients receiving **ERIGE CAPSULES** 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 **ERIGE CAPSULES**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Special Populations:
Because of the extensive cytochrome P450-mediated metabolism of **ERIGE CAPSULES** limited clinical experience in patients with chronic liver disease, caution should be exercised in administering **ERIGE CAPSULES** to patients with liver disease.

Liver Enzymes:
In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended.In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with **ERIGE CAPSULES** needs to be weighed against the unknown risks of significant liver toxicity (see "**Side Effects**").

Cholesterol:
Monitoring of cholesterol and triglycerides should be considered in patients treated with **ERIGE CAPSULES** (see "**Side Effects**").

Paediatric use:
ERIGE CAPSULES has not been studied in paediatric patients below 3 years of age or who weigh less than 40 kg. Therefore, **ERIGE CAPSULES** is not recommended in this group.
ERIGE CAPSULES contains lactose and should not be administered to patients with rare hereditary problems, or a history of lactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption.

Effects on ability to drive and use machines:
ERIGE CAPSULES may cause dizziness, impaired-concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machines.

INTERACTIONS
ERIGE CAPSULES is an inducer of CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with **ERIGE CAPSULES**.

Indinavir:
When indinavir (800 mg every 6 hours) was given with **ERIGE CAPSULES** (200 mg every 24 hours), the indinavir AUC and C_{trough} were decreased by approximately 31 % and 16 % respectively, as a result of enzyme induction. Therefore, the dose of indinavir should be increased from 800 mg to 1 000 mg every 8 hours when **ERIGE CAPSULES** and indinavir are co-administered. No adjustment of the dose of **ERIGE CAPSULES** is necessary when given with indinavir.

Ritonavir:
When **ERIGE CAPSULES** (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) was studied in infected volunteers the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (for example, dizziness, nausea, parasthesia and elevated liver enzymes occurred).
Monitoring of liver enzymes is recommended when **ERIGE CAPSULES** is used in combination with ritonavir.

Saquinavir:
When saquinavir (1 200 mg given 3 times a day, soft capsule formulation) was given with **ERIGE CAPSULES** the saquinavir AUC and C_{max} were decreased by 62 % and 50 % respectively. Use of **ERIGE CAPSULES** in combination with saquinavir as the sole PI is not recommended. **Rifamycins**: Rifampicin reduced **ERIGE CAPSULES** AUC by 26 % and C_{max} by 20 % in 12 uninfected volunteers. The dose of **ERIGE CAPSULES** must be increased to 800 mg/day when taken with rifampin. No dose adjustment of rifampicin is recommended when given with **ERIGE CAPSULES**. Rifabutin has not been studied in combination with **ERIGE CAPSULES**.

Clarithromycin:
Co-administration of 400 mg of **ERIGE CAPSULES** once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C_{max} of clarithromycin decreased 39 % and 26 % respectively, while the AUC and C_{max} of the active clarithromycin hydroxymetabolite were increased 34 % and 49 % respectively, when used in combination with **ERIGE CAPSULES**. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46 % developed rash while receiving **ERIGE CAPSULES** and clarithromycin. No dose adjustment of **ERIGE CAPSULES** is recommended when given with clarithromycin. Alternatives to clarithromycin may be considered.

Oral contraceptives:
Only the ethinyloestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinyloestradiol was increased (37 %) after multiple dosing of **ERIGE CAPSULES**. No significant changes were observed in C_{max} of ethinyloestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyloestradiol on efavirenz C_{max} or AUC was observed. Because the potential interaction of **ERIGE CAPSULES** with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives.

Methadone:
Co-administration of **ERIGE CAPSULES** with methadone, in HIV-infected IV drug users, resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22 % to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

St. John's wort (*Hypericum perforatum*):
Patients on **ERIGE CAPSULES** should not concomitantly use products containing St. John's wort (*Hypericum perforatum*) since it may be expected to result in reduced plasma concentrations of **ERIGE CAPSULES**. This effect is due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance.

Cannabinoid Test interaction:
ERIGE CAPSULES does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received **ERIGE CAPSULES**. False positive test results have only been observed with the CEDIA DAU Multi-Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

PREGNANCY AND LACTATION

Pregnancy:
The use of **ERIGE CAPSULES** during pregnancy is not recommended, as teratogenicity has been noted. Malformations have been observed in foetuses from **ERIGE CAPSULES**-treated monkeys that received doses, which resulted in plasma drug concentrations similar to those in humans given 600 mg/day; therefore pregnancy should be avoided in women receiving **ERIGE CAPSULES**

Women of Childbearing Potential:
Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of **ERIGE CAPSULES** (see **"CONTRAINDICATIONS**").

Lactation:
The safety in lactation has not been established. Since animal data suggest that the substance may be passed into breast milk, it is recommended that mothers taking **ERIGE CAPSULES** do not breast-feed their infants. It is recommended that HIV-infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

DOSAGE AND DIRECTIONS FOR USE

Adults:
The recommended dosage of **ERIGE CAPSULES** in combination with a protease inhibitor, and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily. **ERIGE CAPSULES** may be taken on an empty stomach, preferably at bedtime.
In order to improve the tolerability of nervous system side effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms (see **"Side Effects**").

Concomitant Antiretroviral Therapy:
ERIGE CAPSULES must be given in combination with other antiretroviral medications (see "**Interactions**").
Adolescents and children (17 years and under):
ERIGE CAPSULES may be taken on an empty stomach, at bedtime. **ERIGE CAPSULES** can only be used in adults and children who weigh greater than or equal to 40 kg.

SIDE EFFECTS

Metabolism and nutrition disorders:
The following side effects have been reported and frequencies are unknown: Weight gain and weight loss.

Nervous system disorders:
Frequent: Dizziness, impaired concentration, somnolence, insomnia, aggravated depression.
Less frequent: Abnormal dreams, headache, abnormal/impaired coordination, ataxia, convulsions, hypoesthesia, paraesthesia, neuropathy, peripheral neuropathy, tremors, agitation, amnesia, anxiety, apathy, confusion, emotional lability, euphoria, hallucination, neuralgia, speech disorder, tremor and vertigo.

Eye disorders:
Less frequent: Abnormal vision.

Ear and labyrinth disorders:
Less frequent: Tinnitus.

Cardiac disorders:
Less frequent: Flushing, palpitations and tachycardia.

Respiratory, thoracic and mediastinal disorders:
Less frequent: Asthma, upper respiratory tract infections.
The following side effects have been reported and frequencies are unknown: Sinusitis, dyspnoea.

Gastrointestinal disorders:
Frequent: Nausea, vomiting, diarrhoea.
Less frequent: Anorexia, dyspepsia, abdominal pain, gastritis, gastroenteritis, gastro-oesophageal reflux, taste perversion.
The following side effects have been reported and frequencies are unknown: Appetite increased, constipation and mal-absorption.

Hepato-biliary disorders:
Less frequent: Hepatitis.
The following side effects have been reported and frequencies are unknown: Hepatic enzyme increase and hepatic failure.

Skin and subcutaneous tissue disorders:
Frequent: Rash, pruritus and increased sweating.
Less frequent: Eczema, alopecia, folliculitis, skin exfoliation, urticaria, erythema multiforme, Stevens-Johnson Syndrome.
The following side effects have been reported and frequencies are unknown: Acne, seborrhoea, nail disorders, skin discolouration.

Musculoskeletal, connective tissue and bone disorders:
Less frequent: Arthralgia, myalgia and myopathy.

Reproductive system and breast disorders:
The following side effects have been reported and frequencies are unknown: Impotence, libido decreased, libido increased.

General disorders and administrative site conditions:
Frequent: Fatigue.
The following side effects have been reported and frequencies are unknown: Alcohol intolerance, allergic reaction, asthenia, hot flushes, influenza-like symptoms, malaise, pain, syncope and redistribution/accumulation of body fat.

Investigations:
Less frequent: Raised liver enzyme values have occurred, particularly in patients with viral hepatitis. Raised serum-cholesterol and triglyceride concentrations have been reported.

Liver enzymes:
Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in patients treated with 600 mg of **ERIGE CAPSULES**. Similar elevations were seen in patients treated with control regimens. In 156 patients treated with 600 mg of **ERIGE CAPSULES** who were sero-positive for Hepatitis B and/or C, 7 % developed AST levels and 8 % developed ALT levels greater than five times the upper limit of the normal range. In 91 patients' sero-positive for Hepatitis B and/or C, treated with control regimens, 5 % developed AST elevations and 4 % developed ALT elevations to these levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4 % of all patients treated with 600 mg of **ERIGE CAPSULES** and in 10 % of patients' sero-positive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 1,5 to 2 % irrespective of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving **ERIGE CAPSULES** may reflect enzyme induction not associated with liver toxicity (see "**Warnings and Special Precautions**").

Lipids:
Increases in total cholesterol of 10 to 20 % have been observed in some uninfected volunteers receiving **ERIGE CAPSULES**. Increases in non-fasting total cholesterol and HDL of approximately 20 % and 25 %, respectively were observed in patients treated with efavirenz+ZDV+3TC and of approximately 40 % and 35 %, in patients treated with **ERIGE CAPSULES** +IDV. The effects of **ERIGE CAPSULES** on triglycerides and LDL were not well characterized. The clinical significance of these findings is unknown (see "**Warnings and Special Precautions**").

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms and involuntary muscle contractions. Treatment of overdose with **ERIGE CAPSULES** should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with **ERIGE CAPSULES**. Since **ERIGE CAPSULES** is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

IDENTIFICATION
ERIGE 50 mg CAPSULES:
Yellow/white size '4' hard gelatin capsules imprinted with 'D' on yellow cap and '72' on white body with black edible ink filled with white to off-white coloured powder.
ERIGE 100 mg CAPSULES:
White/white size '2' hard gelatin capsules imprinted with 'D' on white cap and '71' on white body with black edible ink filled with white to off-white coloured powder.
ERIGE 200 mg CAPSULES:
Yellow/yellow size 'OEL' hard gelatin capsules imprinted with 'D' on yellow cap and '36' on yellow body with black edible ink filled with white to off-white coloured powder.

PRESENTATION
ERIGE 50 mg CAPSULES:
Capsules are packed in white, round 40 ml heavy weight HDPE container with 33 mm PP closure with induction sealing wad.
No desiccant is included in the container.
Pack size: 30's: One HDPE container of 30 capsules.
ERIGE 100 mg CAPSULES:
Capsules are packed in white, round 40 ml heavy weight HDPE container with 33 mm PP closure with induction sealing wad.
No desiccant is included in the container.
Pack size: 30's: One HDPE container of 30 capsules.
ERIGE 200 mg CAPSULES:
Capsules are packed in white, round 70 ml heavy weight HDPE container with 43 mm PP closure with induction sealing wad.
No desiccant is included in the container.
Pack size: 30's: One HDPE container of 30 capsules.
Capsules are packed in white, round 200 ml heavy weight HDPE container with 45 mm PP closure with induction sealing wad.
No desiccant is included in the container.
Pack size: 90's: One HDPE container of 90 capsules.

STORAGE INSTRUCTIONS
ERIGE 50 mg CAPSULES, ERIGE 100 mg CAPSULES, ERIGE 200 mg CAPSULES:
Store at or below 30 °C. Protect from light. Keep the container tightly closed.
KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER
ERIGE 50 mg CAPSULES: SOUTH AFRICA: 41/20.2.8/0541
ERIGE 100 mg CAPSULES: SOUTH AFRICA: 41/20.2.8/0542
ERIGE 200 mg CAPSULES: SOUTH AFRICA: 41/20.2.8/0543

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
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DETACH BEFORE DISPENSING

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS
SOUTH AFRICA: S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM
ERIGE 50 mg CAPSULES, efavirenz, 50 mg (capsule).
ERIGE 100 mg CAPSULES, efavirenz, 100 mg (capsule).
ERIGE 200 mg CAPSULES, efavrenz, 200 mg (capsule).

Read all of this leaflet carefully before you start taking ERIGE CAPSULES
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- **ERIGE CAPSULES** 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 ERIGE CAPSULES CONTAINS
- The active substance is Efavirenz.
  - **ERIGE 50 mg CAPSULES:**
    Each capsule contains 50 mg Efavirenz.
  - **ERIGE 100 mg CAPSULES:**
    Each capsule contains 100mg Efavirenz.
  - **ERIGE 200 mg CAPSULES:**
    Each capsule contains 200 mg Efavirenz.
- The other ingredients are: Lactose monohydrate, magnesium stearate, sodium starch glycolate and sodium lauryl sulfate.
- Contains sugar (lactose monohydrate).

2. WHAT ERIGE CAPSULES IS USED FOR
ERIGE CAPSULES are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected adults, adolescents and children weighing greater than or equal to 40 kg.

3. BEFORE YOU TAKE ERIGE CAPSULES
Do not take ERIGE CAPSULES:
- if you are hypersensitive (allergic) to efavirenz or any of the other ingredients of **ERIGE CAPSULES**
- if you are using terfenadine astemizole, cisapride, midazolam, triazolam or ergot derivatives.

This can create the potential for serious and/or life-threatening adverse events [e.g. cardiac arrhythmias, prolonged sedation or respiratory depression].

Take special care with ERIGE CAPSULES:
ERIGE CAPSULES must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. Please consult your doctor, pharmacist or other health care professional for advice.
Monitoring of cholesterol should be considered in patients treated with efavirenz.

Pregnancy and Breastfeeding:
Safety of **ERIGE CAPSULES** in pregnant and lactating women has not been established. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz. The safety in lactation has not been established. It is recommended that HIV-infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

If you are pregnant or breast feeding your baby please consult your doctor, pharmacist or other healthcare professional for advice before taking **ERIGE CAPSULES**.

Driving and using machinery:
Do not drive or operating machinery should you feel sleepy, drowsy, or feel that your concentration is impaired.

Important information about some of the ingredients of ERIGE CAPSULES:
ERIGE CAPSULES contains lactose and should not be administered to patients with rare hereditary problems, or a history of lactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption.

Taking other medicines with ERIGE CAPSULES:
Always tell your healthcare professional if you are taking any other medicines (this includes complementary or traditional medicines).
ERIGE CAPSULES interacts with indinavir, ritonavir, saquinavir, rifampicin, clarithromycin, oral contraceptives, methadone and St. Johns wort.

4. HOW TO TAKE ERIGE CAPSULES
Do not share medicines prescribed for you with any other person.
Always take **ERIGE CAPSULES** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
Your doctor will tell you how long your treatment with **ERIGE CAPSULES** will last.
If you have the impression that the effect of **ERIGE CAPSULES** is too strong or too weak, tell your doctor or pharmacist.

Adults:
The recommended dosage of efavirenz in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily.
Efavirenz may be taken with or without food, as desired. A high fat meal may increase the absorption of efavirenz and should be avoided. In order to improve the tolerability of nervous system side effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms (see **POSSIBLE SIDE EFFECTS**).

Concomitant Antiretroviral Therapy:
ERIGE CAPSULES must be given in combination with other antiretroviral medications (see **Taking other medicines with ERIGE CAPSULES).**

Adolescents and children (17 years and under):
ERIGE CAPSULES may be taken with or without food, as desired. **ERIGE CAPSULES** can only be used in adults and children who weigh greater than or equal to 40 kg.

If you take more ERIGE CAPSULES than you should:
Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms.
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/missed a dose of ERIGE CAPSULES:
Do not take a double dose to make up for forgotten individual doses.

5. POSSIBLE SIDE EFFECTS
ERIGE CAPSULES can have side effects.
Not all side effects reported for **ERIGE CAPSULES** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **ERIGE CAPSULES** please consult your doctor, pharmacist or other healthcare professional for advice.
Efavirenz was generally well tolerated in clinical trials. Efavirenz has been studied in over 9 000 patients. In a subset of 1 008 patients who received 600 mg efavirenz daily in combination with protease inhibitors and/or NRTIs in controlled clinical studies, the most frequently reported treatment- related undesirable effects of at least moderate severity reported in at least 5 % of patients were rash (11,6 %), dizziness (8,5 %), nausea (80 %), headache (5,7 %), and fatigue (5,5 %). Nausea was reported with a higher frequency in the control groups.

The most notable undesirable effects associated with efavirenz are rash and nervous system symptoms.

Other, less frequent, clinically significant treatment-related undesirable effects reported in all clinical trials include: allergic reaction, abnormal coordination, ataxia, confusion, stupor, vertigo, vomiting, diarrhoea, hepatitis, impaired concentration, insomnia, anxiety, abnormal dreams, somnolence, depression, abnormal thinking, agitation, amnesia, delirium, emotional lability, euphoria, hallucination and psychosis.

Additional undesirable effects reported in post-marketing surveillance include neurosis and paranoid reaction, convulsions and blurred vision.

The type and frequency of undesirable effects in children was generally similar to that of adult patients with the exception that rash was reported more frequently in children and was more often of higher grade than in adults.

Rash:
In clinical trials, 26 % of patients treated with 600mg of efavirenz experienced skin rash compared with 17 % of patients treated in control groups. Skin rash was considered treatment-related in 18 % of patients treated with efavirenz. Severe rash occurred in less than 1 % of patients treated with efavirenz and 1,7 % discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson Syndrome was 0,14 %.
Rash was reported in 26 of 57 children (46 %) treated with efavirenz and was severe in 3 patients (5 %). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.
Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with efavirenz. In most patients rash resolves with continuing therapy with efavirenz within one month. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when efavirenz is restarted. Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz, and two discontinued because of rash.

Nervous System Symptoms:
There have been reports (approximately 1 to 2 per thousand efavirenz treated patients) of delusions and inappropriate behaviour, predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both efavirenz treated and control-treated patients. Patients who experience these symptoms should contact their doctor immediately because discontinuation of efavirenz may be required.
Fifty two percent of patients receiving efavirenz reported central nervous system and psychiatric symptoms. These symptoms included, but were not limited to, dizziness, impaired concentration, somnolence, abnormal dreams and insomnia. In controlled trials, these symptoms were severe in 2,0 % of patients receiving efavirenz 600 mg QD and in 1,3 % of patients receiving control regimens. In clinical trials, 2,1 % of efavirenz-treated patients discontinued therapy because of nervous system symptoms. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks. In one clinical study, the monthly prevalence of nervous system symptoms of at least moderate severity between weeks 4 and 45 ranged from 5 % to 9 % in patients treated with regimens containing efavirenz and 3 % to 5 % in patients treated with the control regimen. Patients should be informed that these symptoms are likely to improve with continued therapy. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in patients who continue to experience these symptoms.
Patients receiving **ERIGE CAPSULES** should be altered to the potential for additive central nervous system affects when **ERIGE CAPSULES** is used concomitantly with alcohol or psychoactive drugs.

Patients should be informed that **ERIGE CAPSULES** may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery. Adverse clinical experiences of moderate to severe intensity observed in less than 2 % of patients receiving efavirenz in all Phase II/III studies and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below by body system:

Body as a Whole:
Alcohol intolerance, allergic reaction, asthenia, hot flushes, influenza-like symptoms, malaise, pain and syncope.
Gastrointestinal:
Gastritis, gastroenteritis and gastroesophageal reflux.
Hearing and Vestibular:
Tinnitus.
Cardiovascular:
Blushing, palpitations and tachycardia.
Liver and Biliary System:
Hepatitis.
Metabolic and Nutritional:
Weight gain and weight loss.
Musculoskeletal:
Arthralgia and myalgia.
Nervous System Disorders:
Aggravated depression, agitation, amnesia, anxiety, apathy, appetite increased, ataxia, confusion, emotional lability, euphoria hallucination, impaired coordination, impotence, libido decreased, libido increased, migraine headaches, neuralgia, paraesthesia, peripheral neuropathy, speech disorder, tremor and vertigo.
Respiratory:
Asthma, sinusitis and upper respiratory tract infections.
Skin and Appendages:
Acne, alopecia, eczema, folliculitis, seborrhea, skin exfoliation and urticaria.
Special Senses:
Abnormal vision and taste perversion.

Laboratory Abnormalities:
Raised liver enzyme values have occurred, particularly in patients with viral hepatitis. Raised serum- cholesterol and triglyceride concentrations have been reported.
Liver enzymes: Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in 3 % of 1 008 patients treated with 600 mg of efavirenz. Similar elevations were seen in patients treated with control regimens. In 156 patients treated with 600 mg of efavirenz who were seropositive for Hepatitis B and/or C, 7 % developed AST levels and 8 % developed ALT levels greater than five times the upper limit of the normal range. In 91 patients seropositive for Hepatitis B and/or C, treated with control regimens, 5 % developed AST elevations and 4 % developed ALT elevations to these levels. Elevations of GOT to greater than five times the upper limit of the normal range were observed in 4 % of all patients treated with 600 mg of efavirenz and in 10% of patients seropositive for Hepatitis B or C. In patients treated with control regimens. The incidence of GOT elevations to this level was 1.5 to 2 % irrespective of Hepatitis B or C serology. Isolated elevations of GOT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity.
Lipids: Increases in total cholesterol of 10 to 20 % have been observed in some uninfected volunteers receiving efavirenz. Increases in non-fasting total cholesterol and HDL of approximately 20 % and 25 %, respectively were observed in patients treated with efavirenz+SDV+3TC and of approximately 40 % and 35 %, in patients treated with efavirenz+IDV. The effects of efavirenz on triglycerides and LDL were not well-characterised. The clinical significance of these findings are unknown.
If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF ERIGE CAPSULES
Store at or below 30 °C. Protect from light. Keep the container tightly closed.
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 ERIGE CAPSULES
ERIGE 50 mg CAPSULES:
Capsules are packed in white, round 40 ml heavy weight HDPE container with 33 mm PP closure with induction sealing wad.
No desiccant is included in the container.
Pack size: 30's: One HDPE container of 30 capsules.

ERIGE 100 mg CAPSULES:
Capsules are packed in white, round 40 ml heavy weight HDPE container with 33 mm PP closure with induction sealing wad.
No desiccant is included in the container.
Pack size: 30's: One HDPE container of 30 capsules.

ERIGE 200 mg CAPSULES:
1. Capsules are packed in white, round 70 ml heavy weight HDPE container with 43 mm PP closure with induction sealing wad.

No desiccant is included in the container.
Pack size: 30's: One HDPE container of 30 capsules.

2. Capsules are packed in white, round 200 ml heavy weight HDPE container with 45 mm PP closure with induction sealing wad.

No desiccant is included in the container.
Pack size: 90's: One HDPE container of 90 capsules.

8. IDENTIFICATION OF ERIGE CAPSULES
ERIGE 50 mg CAPSULES:
Yellow/white size '4' hard gelatin capsules imprinted with 'D' on yellow cap and '72' on white body with black edible ink filled with white to off-white coloured powder.
ERIGE 100 mg CAPSULES:
White/white size '2' hard gelatin capsules imprinted with 'D' on white cap and '71' on white body with black edible ink filled with white to off-white coloured powder.
ERIGE 200 mg CAPSULES:
Yellow/yellow size 'OEL' hard gelatin capsules imprinted with 'D' on yellow cap and '36' on yellow body with black edible ink filled with white to off-white coloured powder.

9. REGISTRATION NUMBER
ERIGE 50 mg CAPSULES:
SOUTH AFRICA: 41/20.2.8/0541
ERIGE 100 mg CAPSULES:
SOUTH AFRICA: 41/20.2.8/0542
ERIGE 200 mg CAPSULES:
SOUTH AFRICA: 41/20.2.8/0543

10. NAME AND ADDRESS OF REGISTRATION HOLDER
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NOVAGEN Pharma

PROFESSIONELE INLIGTING

SKEDULERINGSTATUS
SUID-AFRIKA: S4

EIENDOMSNAAM EN DOSERINGSVORM
ERIGE 50 mg CAPSULES (Kapsule)
ERIGE 100 mg CAPSULES (Kapsule)
ERIGE 200 mg CAPSULES (Kapsule)

SAMESTELLING
ERIGE 50 mg CAPSULES:
Elke kapsule bevat 50 mg efavirens.
ERIGE 100 mg CAPSULES:
Elke kapsule bevat 100 mg efavirens.
ERIGE 200 mg CAPSULES:
Elke kapsule bevat 200 mg efavirens.
Eksipiënte: Laktosemonohidraat, magnesiumstearaat, natriumstyselglikolaat en natriumlaurielsulfaat.
Bevat suiker (laktosemonohidraat).

FARMAKOLOGIESE KLASSIFIKASIE
A 20.2.8 Virusteenmiddels

FARMAKOLOGIESE WERKING

Farmakodinamiese eienskappe

Meganisme van werking:
Efavirens is 'n selektiewe nie-nukleosied trutranskriptase-ihibeerder (NNTTI) van die menslike immuun tekort virus tipe I MIV-1. Efavirens diffundeer in die sel waar dit langs die aktiewe plek van trutranskriptase bind. Dit veroorsaak 'n konformasionele verandering in die ensiem en inhibeer sy funksie. Efavirens is 'n nie-kompeterende inhibeerder van MIV-1 trutranskriptase (TT) ten opsigte van die templaat, voorloper of nukleosiedtrifosfate, met 'n klein komponent van kompeterende inhibisie. MIV-2 TT en menslike sellulêre DNA polimerases alfa, beta, gamma en delta word nie deur konsentrasie van efavirens geïnhibeer nie.

***In vitro* MIV vatbaarheid:**
Die kliniese belang van *in vitro* vatbaarheid van MIV-1 teen efavirens is nie vasgestel nie. Die *in vitro* antiviruseffek van efavirens is in limfoblastoïed sellyne, perifere bloed mononukleêre selle (PBMS) en makrofaag-/monosiet kulture, uit PBMS verryk, bepaal. Die 90 – 95% inhibeerderkonsentrasie (IK_{90-95}) van efavirens vir wilde tipe laboratorium aangepaste stamme en kliniese isolate het van 1,7 tot 25 µM gewissel. Efavirens het sinergistiese aktiwiteit in selkultuur in kombinasie met die nukleodied analoog trutranskiptaseïnhibeerders (NTTIs), sidovudien (ZDV) of didanosien (ddi), of die proteaseïnhibeerder, indinavir (IDV), getoon.
In vitro sensitiwiteit impliseer nie noodwendig kliniese sensitiwiteit nie.

Weerstand:
MIV-1 isolater met verlaagde vatbaarheid vir efavirens (meer as 380-voudige toename in IK_{90}) in vergelyking met basislyn kan *in vitro* ontwikkel. Fenotipiese veranderinge in MIV-1 isolate en genotipiese veranderinge in plasmavirus van geselekteerde pasiënte wat met efavirens in kombinasie met IDV of ZDV plus lamivudien behandel is, is gemonitor. Een of meer TT-mutasies by aminosuur posisies 100, 101, 103, 108, 190 en 225 is in al 62 pasiënte met 'n frekwensie van ten minste 10 % in vergelyking met basislyn waargeneem. Vyf kliniese isolate is vir beide genotipiese en fenotipiese veranderinge vanaf basislyn geëvalueer. Afnames in vatbaarheid vir efavirens (wissel van 'n 9- tot meer as 312-voudige toename in IK_{90}) is *in vitro* vir hierdie isolate in vergelyking met basislyn waargeneem. Al vyf isolator het ten minste een van die efavirens ge-assosieerde TT-mutasies besit. Die kliniese betekenis van fenotipiese en genotipiese veranderinge geassosieer met efavirens terapie is nie vasgestel nie.

Kruisweerstand:
Die vinnige ontwikkeling van MIV-1 stamme wat kruisweerstandbiedend teen die nie-nukleosied TT inhibeerders, is *in vitro* waargeneem. Kliniese isolate wat voorheen as efavirensweerstandbiedend gekenmerk is, was ook *in vitro* fenotipies weerstandbiedend teen nevirapien en delavirdien, in vergelyking met basislyn. Klinies verworwe ZDV-weerstandbiedende MIV-1 wat *in vitro* geïsoleer en getoets is, het hul vatbaarheid vir efavirens behou. Kruisweerstand tussen efavirens en MIV-proteaseïnhibeerders is weens die verskillende ensiemteikens wat betrokke is, onwaarskynlik.

__Farmakokinetiese eienskappe:__
Absorpsie:
Piek efavirensplasmakonsentrasie van 1,6 – 9,1 µM is na 5 ure na enkel orale dosisse van 100 mg tot 1 600 mg, toegedien aan onbesmette indiwidue, bereik. Dosisverwante toename in K_{maks} en AOK is waargeneem vir dosisse van tot soveel as 1 600mg, die toenames was minder as proporsioneel, wat dui op 'n agteruitgang van absorpsie teen hoër dosisse. Vastestaat plasmakonsentrasies word binne 6 – 7 dae bereik.

Verspreiding:
Efavirens word sterk aan menslike plasmaproteïene, hoofsaaklik albumien, gebind (ongeveer 99,5 tot 99,7 %). In MIV-1 besmette pasiënte wat efavirens 200 tot 600 mg een keer per dag vir ten minste 'n maand ontvang het, het die konsentrasie in die serebrospinale vloeistof gewissel van 0,26 tot 1,19 % (gemiddeld 0,69 %) van die ooreenstemmende plasmakonsentrasie. Hierdie gedeelte is ongeveer drie keer hoër as die nie- proteïngebonde (vrye) fraksie van efavirens in die plasma.

Metabolisme:
Efavirens word hoofsaaklik deur die sitochroom P450 sisteem gemetaboliseer na gehidroksileerde metaboliete met die daaropvolgende glukuronidasie van hierdie gehidroksileerde metaboliete. Hierdie metaboliete is onaktief teen MIV-1, CYP3A4 en CYP2B6 is die belangrikste isoënsieme wat vir die metabolisme van efavirens verantwoordelik is. Dit is aangetoon dat efavirens P450 ensieme induseer, wat tot die induksie van sy eie metabolisme lei.

Eliminasie:
Efavirens besit 'n lang terminale halfleeftyd van 52 tot 76 ure na enkel dosisse, en 40 - 55 ure na veervuldige dosisse. Ongeveer 14 – 34 % van 'n radiogemerkte dosis efavirens is in die urine herwin, terwyl 16 – 61 % in die feses, hoofsaaklik in die vorm van metaboliete, herwin is.

__Spesiale populasies:__
Belemmerde lewerfunksie:
Die famakokinetika van efavirens is nie voldoende in pasiënte met belemmerde lewerfunksie bestudeer nie.

Belemmerde nierfunsie:
Die famakokinetika van efavirens is nie in pasiente met belemmerde nierfunksie bstudeer nie. Minder as 1 % van efavirens word egter onveranderd in die urine uitgeskei – die impak van belemmerde nierfunksie op die eliminasie van efavirens behoort daarom minimaal te wees.

Geslag en ras:
Dit wil voorkom asof die famakokinetika van efavirens soortgelyk in mans en vroue, asook onder verskillende rasgroepe is.

Pediatriese gebruik:
In 49 pediatriese pasiënte wat die ekwivalent van 'n 600 mg dosis efavirens ontvang het (dosis aangepas volgens die berekende liggaamsgrootte op grond van gewig), was die vastevlak K_{maks} 14,2 µM, die vastevlak K_{min} was 5,6 µM, en AOK was 218 µM. Die famakokinetika van efavirens in pediatriese pasiënte is soortgelyk aan die in volwassenes.

INDIKASIES:
ERIGE CAPSULES in kombinasie met ander anti-retro virus middels, word aangedui vir die behandeling van MIV-1 besmette volwassenes, adolessente en kinders wat 40 kg en meer weeg, en 3 jaar en ouer is.

KONTRA-INDIKASIES:
ERIGE CAPSULES word teenaangedui in pasiënte met 'n hipersensitiwiteit teen **ERIGE CAPSULES** of enige van sy komponente.
ERIGE CAPSULES behoort nie saam met terfenadien, astemisool, kisapried, midasolam, triasolam of ergotderivate toegedien te word nie, aangesien die kompetisie vir CYP3A4 deur efavirens tot 'n inhibisie van die metabolisme van hierdie middels mag lei, wat die potensiaal vir ernstige en/of lewensbedreigende newe-effekte (bv. kardiale disritmieë, verlengde sedering of respiratoriese onderdrukking) mag skep.
Swangerskap en laktasie (sien **"SWANGERSKAP EN LAKTASIE"**).
Kinders jonger as 3 jaar oud of wat minder as 40 kg weeg.

WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS:
Vind uit oor medisyne wat NIE met ERIGE CAPSULES geneem moet word nie (sien "KONTRA-INDIKASIES" en "NEWE-EFFEKTE").
Weerstandige virus stamme ontwikkel vinnig wanneer **ERIGE CAPSULES** as monoterapie toegedien word. Daarom behoort **ERIGE CAPSULES** nie as 'n enkel middel gebruik te word om MIV te behandel nie, of as 'n enkel middel bygevoeg word by 'n regimen wat misluk het.
Ernstige senuweestelsel- en psigiatriese simptome is aangemeld.
Wanneer medisyne saam met **ERIGE CAPSULES** voorgeskryf word, moet geneeshere na die ooreenstemmende produksiesirkulêr verwys. As enige antiretrovirale medikasie in 'n kombinasie-regimen onderbreek word as gevolg van vermoedelike onverdraagsaamheid, moet die gelyktydige staking van alle antiretrovirale medikasie oorweeg word. Die antiretrovirale medisyne moet terselfdertyd weer begin word na die oplossing van die simptome van onverdraagsaamheid. Onderbroke monoterapie en opeenvolgende herbekendstelling van antiretrovirale middels word nie aanbeveel nie as gevolg van die verhoogde potensiaal vir seleksie van 'n geneesmiddelweerstandige mutantvirus.

Lipodistrofie en metaboliese abnormaliteite:
Kombinasie antiretrovirale behandeling is geassosieer met die herverdeling/opeenhoping van liggaamsvet, insluitend sentrale vetsug, dorso-servikale vet, vergroting (buffelbult), perifere uittering, gesigsuittering, borsvergroting en verhoogde serumlipied en glukose vlakke in MIV-pasiënte.
Die kliniese ondersoek moet die fisiese tekens van vetherverdeling insluit. Pasiënte met 'n bewys van lipodistrofie moet 'n deeglike kardiovaskulêre risikobepaling ondergaan.

Veluitslag:
Min tot matige uitslag is gerapporteer met gebruik van **ERIGE CAPSULES** en is normaalweg opgelos met voortgesette terapie. Geskikte antihistamiene en/of kortikosteroïede kan die verdraagsaamheid verbeter en die oplossing van die veluitslag vinniger maak. **ERIGE CAPSULES** moet gestaak word by pasiënte wat ernstige uitslag ontwikkel wat verband hou met blase, afskilfering, mukosale betrokkenheid of koors. As die behandeling met **ERIGE CAPSULES** gestaak word, moet daar ook gekyk word na die onderbreking van die behandeling met ander antiretrovirale middels om die ontwikkeling van 'n middelweerstandige virus te voorkom (sien "**Newe-Effekte**").
Profilakse met toepaslike antihistamiene kan voor behandeling met **ERIGE CAPSULES** by kinders oorweeg word.

Immuunrekonstitusie-inflammatoriese sindroom:
Immuunrekonstitusie-inflammatoriese sindroom (IRIS) is 'n immunopatologiese respons wat voortspruit uit die vinnige herstel van patogeen-spesifieke immuunrespons op bestaande antigene gekombineer met immuun-disregulasie, wat plaasvind kort na die aanvang van die kombinasie van antiretrovirale terapie (cART) . Tipies is sulke reaksies voortspruitend uit paradoksale agteruitgang van opportunistiese infeksies wat behandel word of met die ontmaskering van 'n asimptomatiese opportunistiese siekte, dikwels met 'n atipiese inflammatoriese voorstelling. IRIS ontwikkel gewoonlik binne die eerste drie maande na die aanvang van ART en kom meer gereeld voor by pasiënte met 'n lae CD4-telling. Algemene voorbeelde van IRIS-reaksies op opportunistiese siektes is tuberkulose, sitomegalovirus retinitis en kriptokokkale meningitis.
Die toepaslike behandeling van die opportunistiese siekte moet ingestel word of voortgesit word en ART voortgesit word. Inflammatoriese manifestasies bedaar gewoonlik na 'n paar weke. Erge gevalle reageer moontlik op glukokortikoïede, maar daar is slegs beperkte bewyse hiervan by pasiënte met IRIS van tuberkulose. Auto-immuunafwykings (soos Graves se siekte) is ook as IRIS-reaksies aangemeld; die gerapporteerde tyd tot aanvang is egter meer veranderlik en hierdie gebeure kan baie maande na die aanvang van die behandeling plaasvind.

Simptome van Senuweestelsel:
Simptome van die senuweestelsel is aangemeld met gebruik van **ERIGE CAPSULES** (sien "**Newe-Effekte**"). Daar is ook berigte oor psigose-agtige reaksies, soos misleidings en onvanpaste gedrag (insluitend aggressiewe reaksies), veral by pasiënte met 'n geskiedenis van geestesongesteldheid of dwelmmisbruik. Ernstige akute depressie (insluitend selfmoordgedagtes/-pogings) is ook gereeld by beide **ERIGE CAPSULES**-behandelde en kontrole-behandelde pasiënte gerapporteer, veral by pasiënte met 'n vorige depressiegeskiedenis. Pasiënte moet in kennis gestel word dat as hulle hierdie simptome ervaar, hulle onmiddellik hul dokter moet kontak, omdat die staking van **ERIGE CAPSULES** nodig mag wees.

Osteonekrose:
Alhoewel die etiologie as multifaktoriaal beskou word (insluitend kortikosteroïedgebruik, alkoholverbruik, ernstige immuunonderdrukking, hoër liggaamsmassa-indeks), is gevalle van osteonekrose aangemeld, veral by pasiënte met gevorderde MIV-siekte en/of langtermyn blootstelling aan kombinasie antiretrovirale terapie (cART). Pasiënte moet aangeraai word om mediese advies in te win as hulle gewrigspyne en pyn, gewrigstyfheid of probleme met beweging ervaar.

Opportunistiese infeksies:
Pasiënte wat **ERIGE CAPSULES** ontvang, moet in kennis gestel word dat hulle kan voortgaan met die ontwikkeling van opportunistiese infeksies en ander komplikasies van MIV-infeksie, en daarom moet hulle onder fyn opservasie gehou word deur professionele gesondheidsorgpersoneel wat ervare is in die behandeling van pasiënte met gepaardgaande MIV-siekte. Gereelde monitering van viruslading en CD4-tellings moet gedoen word.

Die risiko van MIV-oordrag aan ander:
Pasiënte moet daarop gewys word dat die huidige antiretrovirale terapie, insluitend **ERIGE CAPSULES**, nie die risiko van oordrag van MIV aan ander deur seksuele kontak of bloedbesmetting voorkom nie. Daar moet voortgegaan word om toepaslike voorsorgmaatreëls te tref.

Spesiale Bevolkings:
Vanweë die uitgebreide sitochroom P450-gemedieërde metabolisme van **ERIGE CAPSULES** beperkte kliniese ondervinding by pasiënte met chroniese lewersiekte, moet versigtigheid toegepas word by die toediening van **ERIGE CAPSULES** aan pasiënte met lewersiekte.

Lewerensieme:
In pasiënte met 'n bekende of vermoedelike geskiedenis van Hepatitis B of C infeksie en by pasiënte wat behandel word met ander medisyne wat met lewertoksisiteit verband hou, word die monitering van lewerensieme aanbeveel.
In pasiënte met 'n aanhoudende verhoging van serumtransaminases tot meer as 5 keer die boonste limiet van die normale omvang, moet die voordeel van voortgesette terapie met **ERIGE CAPSULES** opgeweeg word teen die onbekende risiko's van beduidende lewertoksisiteit (sien "**Newe-Effekte**").

Cholesterol:
Monitering van cholesterol en trigliseriede moet oorweeg word by pasiënte wat met **ERIGE CAPSULES** behandel word (sien "**Newe-Effekte**").
Pediatriese gebruik:
ERIGE CAPSULES is nie bestudeer by kinders onder 3 jaar nie, of wat minder as 40 kg weeg nie. Daarom word **ERIGE CAPSULES** nie in hierdie groep aanbeveel nie.
ERIGE CAPSULES bevat laktose en moet nie toegedien word aan pasiënte met seldsame oorerflike probleme, of 'n geskiedenis van laktose-intoleransie, Lapp laktose-tekort of glukose-galaktose wanabsorpsie nie.

Effekte op die bestuur en bestuur van masjiene:
ERIGE CAPSULES kan duiseligheid, verswakte konsentrasie en/of slaperigheid veroorsaak. Pasiënte moet opdrag gegee word dat, as hulle hierdie simptome ervaar, hulle potensieel gevaarlike take soos bestuur of bestuur van masjiene moet vermy.

INTERAKSIES:
ERIGE CAPSULES is 'n induseerder van CYP3A4. Ander verbindings wat 'n substraat van CYP3A4 is, mag laer plamakonsentrasies he wanneer dit saam met **ERIGE CAPSULES** toegedien word.
Indinavir:
Wanneer indinavir (800 mg elke 8 ure) saam met **ERIGE CAPSULES** (200 mg elke 24 ure) toegedien is, het die AOK en K_{trog}, weens ensieminduksie, met ongeveer 31 % en 16 % respektiewelik afgeneem. Geen dosisaanpassing van **ERIGE CAPSULES** is nodig wanneer dit saam met indinavir toegedien word nie.

Ritonavir:
Toe **ERIGE CAPSULES** (een keer per dag toegedien met slapenstyd) en ritonavir 500 mg (elke 12 ure toegedien) in besmette vrywilligers bestudeer is, is die kombinasie nie goed verdra nie en het dit met 'n hoër frekwensie van kliniese newe-effekte (bv. duiseligheid, naarheid, parestesie en 'n toename in lewer ensieme het voorgekom) gepaard gegaan.
Die monitering van lewer ensieme word aanbeveel wanneer **ERIGE CAPSULES** in kombinasie met ritonavir gebruik word.

Sakinavir:
Toe sakinavir (1 200mg, sagte kapsuleformulasie, 3 keer per dag) saam met **ERIGE CAPSULES** toegedien is, het die sakinavir AOK en K_{maks} met 62 % en 50 % respektiewelik afgeneem. Die gebruik van **ERIGE CAPSULES** in kombinasie met sakinavir as die enigste PI word nie aanbeveel nie.

Rifampisien:
Rifampisien het die AOK van **ERIGE CAPSULES** met 26 % en die K_{maks} met 20 % in 12 onbesmette vrywilligers laat afneem. Die **ERIGE CAPSULES** dosis moet na 800 mg/dag verhoog word wanneer dit saam met rifampisien gebruik word. Geen dosisaanpassing vir rifampisien word aanbeveel wanneer dit saam met **ERIGE CAPSULES** gebruik word nie. Rifabutien is nie in kombinasie met **ERIGE CAPSULES** bestudeer nie.

Klaritromisien:
Die medetoediening van 400 mg **ERIGE CAPSULES** een keer per dag met klaritromisien as 500 mg elke 12 ure sewe dae het tot 'n aansienlike effek van efavirens op die farmakokinetika van klaritromisien gelei. Die AOK en K_{maks} van klaritromisien het met 39 % en 26 % respektiewelik afgeneem terwyl die AOK en K_{maks} van die aktiewe klaritromisien hidroksiemetaboliet met 34 % en 49 % respektiewelik toegeneem het wanneer in kombinasie met **ERIGE CAPSULES** gebruik is. Die kliniese betekenis van hierdie veranderinge in die plasmavlakke van klaritomisien is nie bekend nie. In onbesmette vrywilligers het 46 % uitslag ontwikkel terwyl hulle **ERIGE CAPSULES** en klaritomisien ontvang het. Geen dosisaanpassings van **ERIGE CAPSULES** word aanbeveel wanneer dit saam met klaritromisien toegedien word nie. Alternatiewe tot klaritromisien mag oorweeg word.

Orale voorbehoedmiddels:
Slegs die etinielestradiol komponent van orale voorbehoedmiddels is bestudeer. Die AOK na 'n enkel dosis etinielestradiol het toegeneem (37 %) na veelvuldige dosisse van **ERIGE CAPSULES**. Geen noemenswaardige veranderinge is in die K_{maks} van etinielestradiol waargeneem nie. Die kliniese betekenis van hierdie effekte is nie bekend nie. Geen effek van 'n enkel dosis etinielestradiol op die K_{maks} of AOK van efavirens is waargeneem nie. Aangesien die potensiële interaksie van **ERIGE CAPSULES** met orale voorbehoedmiddels nie ten volle bestudeer is nie, behoort 'n betroubare metode van skeidingsvoorbehoeding, bo en behalwe orale voorbehoeding, gebruik te word.

Metadoon:
Die medetoediening van **ERIGE CAPSULES** met metadoon in MIV-besmette persone wat IV dwelms gebruik, het tot 'n afname in plasmavlakke van metadoon en tekens van opiaatonttrekking gelei. Die matadoondosis is met 'n gemiddeld van 22 % verhoog om die onttrekkingsimptome te verlig. Pasiënte behoort vir tekens van onttrekking gemonitor te word en hul metadoondosis behoort verhoog te word om die onttrekkingsimptome te verlig.

St, John se kruid *(Hypericum perforatum):*
Pasiënte op **ERIGE CAPSULES** behoort nie terselfdertyd produkte wat St. John se kruid *(Hypericum perforatum)* te gebruik nie, aangesien daar verwag word dat dit tot 'n afname in plasmakonsentrasie van **ERIGE CAPSULES** mag lei. Hierdie effek is weens 'n induksie van CYP3A4 en mag tot 'n verlies aan die terapeutiese effek en die ontwikkeling van weerstand lei.

Kannabinoïed Toetsinteraksie:
ERIGE CAPSULES bind nie aan kannabinoïedreseptore nie. Vals positiewe urienkannabinoïed toetsresultate is in onbesmette vrywilligers wat **ERIGE CAPSULES** ontvang het, aangemeld. Vals positiewe toetresultate is slegs waargeneem met die CEDIA DAU Multivlak THC-bepaling, wat vir sifting gebruik word, en is nie met ander kannabinoïed bepalings, insluitend toetse wat vir die bevestiging van positiewe resultate gebruik word, waargeneem nie.

SWANGERSKAP EN LAKTASIE:

Swangerskap:
Die gebruik van **ERIGE CAPSULES** word nie gedurende swangerskap en laktasie aanbeveel nie, aangesien teratogenisiteit opgemerk is. Wanvorming is waargeneem in fetusse van **ERIGE CAPSULES** behandelde apies wat dosisse ontvang het wat plasmakonsentrasies van die middel gelewer het, soortgelyk aan die in mense wat 600 mg per dag ontvang het. Swangerskap behoort daarom vermy te word in vroue wat **ERIGE CAPSULES** ontvang.

Vroue van barensmoondheid:
Skeidingsvoorbehoeding behoort altyd in kombinasie met ander metodes van voorbehoeding (bv, orale of ander hormonale voorbehoeding) gebruik te word. Vroue van barensmoondheid behoort 'n swangerskaptoets voor die inisiëring van **ERIGE CAPSULES** te ondergaan (sien: **"KONTRA-INDIKASIES"**).

Laktasie:
Die veiligheid in laktasie is nie vasgestel nie. Aangesien dieredata daarop dui dat die middel na moedersmelk mag versprei, word dit aanbeveel dat moeders wat **ERIGE CAPSULES** gebruik, nie hul babas borsvoed nie. Dit word aanbeveel dat MIV-besmette moeders nie hul babas onder geen omstandighede borsvoed nie, om die oordraging van MIV te voorkom.

DOSIS EN GEBRUIKSAANWYSINGS:

Volwassenes:
Die aanbevole **ERIGE CAPSULES** dosis in kombinasie met 'n proteaseïnhibeerder, en/of nukleosied analoogtrutranskripaseïnhibeerders (NTTI's) is 600 mg een keer per dag. **ERIGE CAPSULES** mag op 'n leë maag geneem word, verkieslik met slapensyd.
Om die verdraagsaamheid van newe-effekte van die senuweestelsel te verbeter, word dosering met slapensyd vir die eerste twee tot vier weke van terapie aanbeveel, asook in pasïente wat aanhou om hierdie simptome te ondervind (sien **"NEWE-EFFEKTE"**).

Meegaande Antiretrovirusterapie:
ERIGE CAPSULES moet in kombinasie met ander anti-retro virus middels toegedien word (sien **"INTERAKSIES"**).
Adolessente en kinders (jonger as 17 jaar):
ERIGE CAPSULES 600 mg behoort slegs in volwassenes en kinders wat 40 kg of meer weeg, gebruik te word.

NEWE-EFFEKTE
__Afwykings van die metabolisme en voeding__
Die volgende newe-effekte is aangemeld en die frekwensies is onbekend: Massatoename en –verlies.
__Afwykings van die senuweestelsel__
Dikwels: Duiseligheid, belemmerde konsentrasie, slaapsug, slaaploosheid, verdiepte depressie.
Minder dikwels: Abnormale drome, hoofpyn, abnormale/belemmerde koördinasie, ataksie, stuiptrekkings, hipoëstesie, parestesie, neuropatie, perifere neuropatie, bewerasie, agitasie, geheuverlies, angs, apatie, verwardheid, emosionele onstabiliteit, euforie, hallusinering, neuralgie, spraakafwyking, bewerasie en vertigo.
__Oogafwykings__
Minder dikwels: Abnormale visie
__Afwykings van die oor en labirint__
Minder dikwels: Tinnitus
__Hartafwykings__
Minder dikwels: Hittegloede, hartkloppings en tagikardie
__Respiratoriese, bors- en mediastinale afwykings__
Minder dikwels: Asma, boonste lugweginfeksies.
Die volgende newe-effekte is aangemeld en die frekwensies is onbekend: Sinusitis, dispnee
__Gastroïntestinale afwykings__
Dikwels: Naarheid, braking, diaree
Minder dikwels: Anoreksie, dispepsie, buikpyn, gastritis, gastroënteritis, gastro-esofagale refluks, smaakafwyking.
Die volgende newe-effekte is aangemeld en die frekwensies is onbekend: Toename in eetlus, hardlywigheid en wanabsorpsie.
__Hepato-bileêre afwykings__
Minder dikwels: Hepatitis
Die volgende newe-effekte is aangemeld en die frekwensie is onbekend: Toename in lewer ensieme en lewerversaking.
__Afwykings van die vel en subkutane weefsel__
Dikwels: Uitslag, pruritus en toename in sweet
Minder dikwels: Ekseem, alopesie, follikulitis, velafskilfering, urtikarie, erythema muliforme, Stevens-Johnson se sindroom.
Die volgende newe-effekte is aangemeld en die frekwensies is onbekend: Aknee, seborree, naelafwykings, velverkleuring.
__Muskulosketale, bindweefsel- en beenafwykings__
Minder dikwels: Artralgie, mialgie en miopatie
__Afwykings van die reproduksiestelsel en bors__
Die volgende newe-effekte is aangemeld en die frekwensie is onbekend: Impotensie, afname in libido, toename in libido.
__Algemene afwykings en kondisies by die plek van aanwending__
Dikwels: Moegheid
Die volgende newe-effekte is aangemeld en die frekwensies is onbekend: Alkoholintoleransie, allergiese reaksie, astenie, hittegloede, griepagtige simptome, malaise, pyn, sinkopee en herverspreiding/akkumulasie van liggaamsvet.
__Ondersoeke__
Minder dikwels: Verhoogde lewer ensiem waardes het voorgekom, veral in pasiënte met virus hepatitis. 'n Toename in serum cholesterol- en trigliseriedkonsentrasies is aangemeld.
Soortgelyke verhogings is gesien by pasiënte wat met kontrole behandelings behandel is. In 156 pasiënte wat met 600 mg **ERIGE CAPSULES** behandel is en wat sero-positief was vir Hepatitis B en/of C, het 7 % AST-vlakke ontwikkel, en 8 % het ALT-vlakke ontwikkel groter as vyf keer die boonste limiet van die normale reeks. By 91 pasiënte wat sero-positief was vir Hepatitis B en/of C, wat behandel was met kontrole regimente, het 5 % AST-verhogings ontwikkel en 4 % het ALT-verhogings ontwikkel tot hierdie vlakke. Verhogings van GGT tot meer as vyf keer die boonste limiet van die normale omvang is waargeneem by 4 % van alle pasiënte wat met 600 mg **ERIGE CAPSULES** behandel is, en in 10 % van die pasiënte wat sero-positief was vir Hepatitis B of C. By pasiënte wat behandel was met kontrole regimente, was die voorkoms van GGT-verhogings tot op hierdie vlak 1,5 tot 2 %, ongeag die serologie van Hepatitis B of C. Geïsoleerde verhogings van GGT by pasiënte wat **ERIGE CAPSULES** ontvang, kan die induksie van ensiem weerspieël wat nie met lewertoksisiteit verband hou nie (sien **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).

Lewer ensieme:
Toenames in AST en ALT na meer as vyf keer die boonste limiet van normaal is in pasiënte wat met 600 mg **ERIGE CAPSULES** behandel is, waargeneem.
Lipiede:
Toenames van 10 tot 20 % in totale cholesterol is in sommige onbesmette vrywilligers wat **ERIGE CAPSULES** ontvang het, waargeneem. Toenames in nie-vastende totale cholesterol en HDL van ongeveer 20 % tot 25 % respektiewelik, is in pasiënte wat met efavirens + SDV +3TC behandel is, waargeneem en van ongeveer 40 % tot 35 % in pasiënte wat met **ERIGE CAPSULES** + IDV behandel is. Die effek van **ERIGE CAPSULES** op trigliseriede en LDL is nie goed beskryf nie. Die kliniese betekenis van hierdie bevindings is onbekend (sien **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN
Sommige pasiënte wat per ongeluk 600 mg twee keer per dag geneem het, het 'n toename in simptome van die senuweestelsel en onwillekeurige spierkontraksies aangemeld. Die behandeling van oordosering met **ERIGE CAPSULES** behoort uit algemene ondersteunende maatreëls, insluitend die monitering van lewenstekens en observasie van die pasiënt se kliniese status, te bestaan. Die toediening van geaktiveerde houtskool kan gebruik word om die ongeabsorbeerde middel te verwyder. Daar is geen spesifieke teenmiddel vir oordosering met **ERIGE CAPSULES** nie. Aangesien **ERIGE CAPSULES** hoogs proteïengebonde is, is dit onwaarskynlik dat die middel tot enige noemenswaardige mate deur dialise uit die bloed verwyder word.

IDENTIFIKASIE:
ERIGE 50 mg CAPSULES
Geel/wit grootte '4' harde gelatien kapsules met 'D' op die geel dop en '72' op die wit liggaam met swart voedselgraad ink daarop gedruk, gevul met 'n wit tot naaswit poeier.
ERIGE 100 mg CAPSULES
Wit/wit grootte '2' harde gelatien kapsules met 'D' op die wit dop en '71' op die wit liggaam met swart voedselgraad ink daarop gedruk, gevul met 'n wit tot naaswit poeier.
ERIGE 200 mg CAPSULES
Geel/geel grootte 'OEL' harde gelatien kapsules met 'D' op die geel dop en '36' op die geel liggaam met swart voedselgraad ink daarop gedruk, gevul met 'n wit tot naaswit poeier.

AANBIEDING:
ERIGE 50 mg CAPSULES:
__**HDPE Houer:**__
1. Die kapsules word in 'n wit, ronde 40 ml, swaargewig HDPE houer met 'n 33 mm PP-deksel en 'n induksie seëlprop verpak.

Geen droogmiddel is in die houer ingesluit nie.
__Pakgrootte:__ 30's: Elke houer bevat 30 kapsules

ERIGE 100 mg CAPSULES:
__**HDPE Houer:**__
1. Die kapsules word in 'n wit, ronde 40 ml, swaargewig HDPE houer met 'n 33 mm PP-deksel en 'n induksie seëlprop verpak.

Geen droogmiddel is in die houer ingesluit nie.
__Pakgrootte:__ 30's: Elke houer bevat 30 kapsules

ERIGE 200 mg CAPSULES:
__**HDPE Houer:**__
1. Die kapsules word in 'n wit, ronde 70 ml, swaargewig HDPE houer met 'n 33mm PP-deksel en 'n induksie seëlprop verpak.

Geen droogmiddel is in die houer ingesluit nie.
__Pakgrootte:__ 30's: Elke houer bevat 30 kapsules

2. Die kapsules word in 'n wit, ronde 200ml swaargewig swaargewig HDPE houer met 'n 45 mm PP-deksel en 'n induksie seëlprop verpak.

Geen droogmiddel is in die houer ingesluit nie.
__Pakgrootte:__ 90's: Elke houer bevat 90 kapsules.

BERGINGSINSTRUKSIES

ERIGE 50 mg CAPSULES, ERIGE 100 mg CAPSULES, ERIGE 200 mg CAPSULES
Bewaar benede 30 °C. Beskerm teen lig, Hou die houer dig toe.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:
ERIGE 50 mg CAPSULES SUID-AFRIKA: 41/20.2.8/0541
ERIGE 100 mg CAPSULES SUID-AFRIKA: 41/20.2.8/0542
ERIGE 200 mg CAPSULES SUID-AFRIKA: 41/20.2.8/0543

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:
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Nellmapiusrylaan
Irene – Pretoria
Suid-Afrika

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P1522657

DETACH BEFORE DISPENSING

PASIËNTINLIGTINGSBILJET

SKEDULERINGSTATUS
SUID-AFRIKA: S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM
ERIGE 50 mg CAPSULES, **efavirens**, 50 mg (kapsule).
ERIGE 100 mg CAPSULES, **efavirens**, 100 mg (kapsule).
ERIGE 200 mg CAPSULES, **efavirens**, 200 mg (kapsule).

Lees die hele biljet sorgvuldig deur voordat u met ERIGE CAPSULES begin
- Bewaar hierdie biljet. Miskien moet u dit weer lees.
- Vra u dokter of apteker as u nog vrae het.
- **ERIGE CAPSULES** is persoonlik vir u voorgeskryf en u moet nie u medisyne met ander mense deel nie. Dit kan hulle benadeel, selfs as hul simptome dieselfde is as joune.

1. WAT ERIGE CAPSULES BEVAT
- Die aktiewe bestanddeel is Efavirens.
  - **ERIGE 50 mg CAPSULES:** Elke kapsule bevat 50 mg Efavirens.
  - **ERIGE 100 mg CAPSULES:** Elke kapsule bevat 100 mg Efavirens.
  - **ERIGE 200 mg CAPSULES:** Elke kapsule bevat 200 mg Efavirens.
- Die ander bestanddele is: Laktosemonohidraat, magnesiumstearaat, natriumstyselglikolaat en natriumlaurielsulfaat.
- Bevat suiker (laktosemonohidraat).

2. WAT ERIGE CAPSULES VOOR GEBRUIK WORD
ERIGE CAPSULES word aangedui in kombinasie met ander antiretrovirale middels vir die behandeling van MIV-1 besmette volwassenes, adolessente en kinders wat meer as, of 40 kg weeg.

3. VOORDAT U ERIGE CAPSULES NEEM
Moenie ERIGE CAPSULES neem:
- as u hipersensitief (allergies) vir efavirens of een van die ander bestanddele van **ERIGE CAPSULES** is nie
- as u terfenadien astemisool, sisapried, midasolam, triasolam of ergotderivate gebruik. Dit kan die potensiaal skep vir ernstige en/of lewensgevaarlike nadelige gebeure [bv. hartaritmieë, langdurige kalmering of respiratoriese depressie].

Wees veral versigtig met ERIGE CAPSULES:
ERIGE CAPSULES moet nie as 'n enkele middel gebruik word om MIV te behandel nie, of as 'n enigste middel by 'n mislukte regimen gevoeg word nie. Raadpleeg u dokter, apteker of ander gesondheidsorgwerker vir advies.
Monitering van cholesterol moet oorweeg word by pasiënte wat met efavirens behandel word.

Swangerskap en borsvoeding:
Die veiligheid van **ERIGE CAPSULES** by swanger en lakterende vroue is nie vasgestel nie. Vroue met swangerskap-moontlikheid moet swangerskapstoetse ondergaan voordat hulle met efavirens begin. Die veiligheid tydens laktasie is nie vasgestel nie. Dit word aanbeveel dat MIV-geïnfekteerde vroue onder geen omstandighede hul babas borsvoed nie om MIV-oordrag te voorkom.

As u swanger is of u baba borsvoed, raadpleeg u dokter, apteker of ander professionele gesondheidsorgwerker voordat u **ERIGE CAPSULES** neem.

Bestuur en gebruik van masjinerie:
Moet nie bestuur of masjinerie gebruik as u slaperig of lomerig voel of voel dat u konsentrasie nie meer goed is nie.

Belangrike inligting oor sommige van die bestanddele van ERIGE CAPSULES:
ERIGE CAPSULES bevat laktose en moet nie toegedien word aan pasiënte met seldsame oorerflike probleme, of 'n geskiedenis van laktose-intoleransie, Lapp laktose-tekort of glukose-galaktose wanabsorpsie nie.

Neem van ander medisyne saam met ERIGE CAPSULES
Vertel altyd u gesondheidssorgwerker as u enige ander medisyne neem (dit sluit komplementêre of tradisionele medisyne in).
ERIGE CAPSULES het 'n interaksie met indinavir, ritonavir, sakwinavir, rifampisien, klaritromisien, orale voorbehoedmiddels, metadoon en St. Johns-wort.

4. HOE OM ERIGE CAPSULES TE NEEM
Moenie medisyne wat vir u voorgeskryf is, met enige ander persoon deel nie.
Neem altyd **ERIGE CAPSULES** presies soos deur u dokter opdrag gegee is. U moet dit met u dokter of apteker nagaan as u onseker is.
U dokter sal u vertel hoe lank u behandeling met **ERIGE CAPSULES** sal duur.
Vertel u dokter of apteker as u die indruk het dat die effek van **ERIGE CAPSULES** te sterk of te swak is.

Volwassenes:
Die aanbevole dosering efavirens in kombinasie met 'n protease-remmer en/of nukleosied analoog omgekeerde transkriptase-remmer (NRTI's) is 600 mg oraal, een keer per dag.
Efavirens kan geneem word met of sonder voedsel, na wense. 'n Maaltyd met hoë vet kan die opname van efavirens verhoog en dit moet vermy word. Ten einde die verdraagsaamheid van newe-effekte van die senuweestelsel te verbeter, word die dosering aanbeveel voor bedtyd gedurende die eerste twee tot vier weke van terapie en by pasiënte wat aanhou om hierdie simptome te ervaar (sien **MOONTLIKE NEWE-EFFEKTE**).

Gelyktydige antiretrovirale terapie:
ERIGE CAPSULES moet gegee word in kombinasie met ander antiretrovirale medisyne (sien **Gebruik van ander medisyne saam met ERIGE CAPSULES).**

Adolessente en kinders (17 jaar en jonger):
ERIGE CAPSULES kan geneem word met of sonder voedsel, na wense. **ERIGE CAPSULES** kan slegs gebruik word by volwassenes en kinders wat 40 kg en meer weeg.

As u meer ERIGE CAPSULES neem as wat u moes:
Sommige pasiënte wat per ongeluk 600 mg twee keer per dag inneem, het verhoogde simptome van die senuweestelsel gerapporteer.
In geval van oordosering, raadpleeg u dokter of apteker. As daar nie een beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.

As u vergeet het om 'n dosis ERIGE CAPSULES te neem/gemis het:
Moenie 'n dubbele dosis neem om op te maak vir die vergete dosis nie.

5. MOONTLIKE NEWE-EFFEKTE
ERIGE CAPSULES kan newe-effekte hê.
Nie alle newe-effekte wat vir **ERIGE CAPSULES** aangemeld is, is in hierdie biljet ingesluit nie. Raadpleeg u dokter, apteker of ander gesondheidsorgwerker vir advies indien u algemene gesondheid vererger, of as u slegte gevolge ondervind terwyl u **ERIGE CAPSULES** neem.
Efavirens is oor die algemeen goed verdra in kliniese proewe. Efavirens is bestudeer by meer as 9 000 pasiënte. In 'n subgroep van 1 008 pasiënte wat daagliks 600 mg efavirens in kombinasie met protease-remmers en/of NRTI's ontvang het, was die mees dikwelse gerapporteerde ongewenste effekte van ten minste 5 % van die pasiënte wat behandel is, uitslag (11,6 %), duiseligheid (8,5 %), naarheid (80 %), hoofpyn (5,7 %) en moegheid (5,5 %). Naarheid is met 'n hoër frekwensie in die kontrolegroepe aangemeld.

Die mees noemenswaardige newe-effekte wat met efavirens verband hou, is veluitslag en senuweestelsel simptome.

Ander, minder dikwels, klinies beduidende behandelingsverwante ongewenste effekte wat in alle kliniese proewe gerapporteer is, sluit in: allergiese reaksie, abnormale koördinasie, ataksie, verwarring, bedwelmheid, vertigo, braking, diarree, hepatitis, verminderde konsentrasie, slapeloosheid, angs, abnormale drome, slaperigheid, depressie, abnormale denke, agitasie, amnesie, delirium, emosionele labiliteit, euforie, hallusinasie en psigose.

Bykomende ongewenste gevolge wat tydens die bemarking na bemarking gerapporteer word, is neurose en paranoïede reaksie, stuiptrekkings en dowwe visie.

Die tipe en frekwensie van die ongewenste effekte by kinders was oor die algemeen dieselfde as by volwasse pasiënte, met die uitsondering dat uitslag meer gereeld by kinders gerapporteer word en meer gereeld van 'n hoër graad as by volwassenes was.

__Uitslag:__
In kliniese studies het 26 % van die pasiënte wat met 600 mg efavirens behandel is, veluitslag ervaar, vergeleke met 17 % van die pasiënte wat in kontrolegroepe behandel is. Veluitslag is as behandelingsverwant beskou by 18 % van die pasiënte wat met efavirens behandel is. Ernstige uitslag het voorgekom by minder as 1 % van die pasiënte wat met efavirens behandel is, en 1,7 % het die behandeling gestaak weens uitslag. Die voorkoms van erythema multiforme of Stevens-Johnson-sindroom was 0,14 %.
Uitslag is aangemeld by 26 van 57 kinders (46 %) wat met efavirens behandel is en was ernstig by 3 pasiënte (5 %). Profilakse met toepaslike antihistamiene voordat die behandeling met efavirens by kinders begin word, kan oorweeg word.
Uitslag is gewoonlik ligte tot matige makulopapulêre veluitbarstings wat plaasvind binne die eerste twee weke nadat die behandeling met efavirens begin is. By die meeste pasiënte is die uitslag opgelos binne 'n maand met voortgesette terapie met efavirens. Efavirens kan weer ingestel word by pasiënte wat terapie onderbreek weens uitslag. Die gebruik van toepaslike antihistamiene en / of kortikosteroïede word aanbeveel wanneer weer met efavirens begin word. Ervaring met efavirens by pasiënte wat ander antiretrovirale middels van die NNRTI-klas gestaak het, is beperk. Negentien pasiënte wat nevirapien gestaak het weens uitslag, is met efavirens behandel. Nege van hierdie pasiënte het ligte tot matige uitslag ontwikkel tydens die behandeling met efavirens, en twee is gestaak weens uitslag.

__Simptome van die Senuweestelsel:__
Daar is al gerapporteer (ongeveer 1 tot 2 per duisend pasiënte wat behandel is met efavirens) van wanvoorstellings en onvanpaste gedrag, veral by pasiënte met 'n geskiedenis van geestesongesteldheid of dwelmmisbruik. Ernstige akute depressie (insluitend selfmoord-idees/-pogings) is ook selde by beide pasiënte wat met efavirens behandel gerapporteer. Pasiënte wat hierdie simptome ervaar, moet onmiddellik hul dokter kontak, want dit kan nodig wees om efavirens te stop.
Twee en vyftig persent van pasiënte wat efavirens ontvang, het sentrale senuweestelsel en psigiatriese simptome aangemeld. Hierdie simptome sluit in, maar was nie beperk nie tot, duiseligheid, verminderde konsentrasie, slaperigheid, abnormale drome en slapeloosheid. In gekontroleerde toetse was hierdie simptome ernstig by 2,0 % van pasiënte wat efavirens 600 mg QD ontvang het, en by 1,3 % van die pasiënte wat kontrole-behandeling ontvang het. In kliniese studies het 2,1 % van die pasiënte wat met efavirens behandel is, die behandeling gestaak weens simptome van die senuweestelsel. Hierdie simptome begin gewoonlik gedurende die eerste of tweede dag van terapie en klaar gewoonlik na die eerste 2 tot 4 weke op. In een kliniese studie het die maandelikse voorkoms van simptome van die senuweestelsel van ten minste matige erns tussen week 4 en 45 gewissel van 5 % tot 9 % by pasiënte wat behandel is met regimen wat efavirens bevat en 3 % tot 5 % in pasiënte wat behandel is met die kontrole-behandeling. Pasiënte moet ingelig word dat hierdie simptome waarskynlik sal verbeter met voortgesette terapie. Dosering teen bedtyd verhoog die verdraagsaamheid van hierdie simptome en word aanbeveel gedurende die eerste weke van terapie en by pasiënte wat aanhou om hierdie simptome te ondervind
Pasiënte wat **ERIGE CAPSULES** ontvang, moet verander word vir die potensiële addisionele sentrale senuweestelsel gevolge wanneer **ERIGE CAPSULES** tesame met alkohol of psigo-aktiewe middels gebruik word.

Pasiënte moet in kennis gestel word dat **ERIGE CAPSULES** duiseligheid, verswakte konsentrasie en/of slaperigheid kan veroorsaak. Pasiënte moet opdrag gegee word dat, indien hulle hierdie simptome ervaar, hulle potensieel gevaarlike take soos bestuur of bestuur van masjinerie moet vermy. Nadelige kliniese ervarings van matige tot ernstige intensiteit is waargeneem in minder as 2 % van die pasiënte wat efavirens ontvang in alle fase II/III-studies, wat as ten minste moontlik verwant is of onbekende verwantskap het met behandeling en van ten minste matige erns beskou word, word hieronder deur die liggaamstelsel gelys:

__Liggaam as 'n geheel:__
Alkoholverdraagsaamheid, allergiese reaksie, astenie, warm gloede, griepagtige simptome, malaise, pyn en sinkopee.
__Maag:__
Gastritis, gastroënteritis en gastro-esofageale refluks.
__Gehoor en vestibulêr:__
Tinnitus.
__Kardiovaskulêr:__
Blosing, hartkloppings en tagikardie.
__Lewer- en galstelsel:__
Geelsug.
__Metaboliese en Voedingswaarde:__
Gewigstoename en gewigsverlies.
__Muskuloskeletale:__
Artralgie en mialgie.
__Senuweestelselafwykings:__
Verergerde depressie, agitasie, amnesie, angs, apatie, verhoogde aptyt, ataksie, verwarring, emosionele vermoëns, euforie hallusinasie, verswakte koördinasie, impotensie, verminderde libido, verhoogde libido, migraine hoofpyn, neuralgie, paraestesie, perifere neuropatie, spraakversteuring, bewing en vertigo .
__Respiratories:__
Asma, sinusitis en infeksies in die boonste lugweg.
__Vel en aanhangsels:__
Aknee, alopesie, ekseem, follikulitis, seborree, velafskilfering en urtikarie.
__Spesiale sintuie:__
Abnormale sig en smaakafwyking.
__Laboratoriumafwykings:__
Verhoogde lewerensiemwaardes het voorgekom, veral by pasiënte met virale hepatitis. Verhoogde konsentrasies in serum- cholesterol en trigliseriede is aangemeld.
Lewerensieme: Die verhoging van AST en ALT tot meer as vyf keer die boonste limiet van die normale omvang is gesien by 3 % van die 1 008 pasiënte wat met 600 mg efavirens behandel is. Soortgelyke verhogings is ook gesien by pasiënte wat met kontrole-behandelings behandel is. In 156 pasiënte wat behandel is met 600 mg efavirens wat seropositief was vir Hepatitis B en/of C, het 7 % AST-vlakke ontwikkel en 8 % het ALT-vlakke groter as vyf keer die boonste limiet van die normale reeks. By 91 pasiënte wat seropositief is vir Hepatitis B en/of C, behandel met kontrole-regimen, het 5 % AST-verhogings ontwikkel en 4 % het ALT-verhogings tot hierdie vlakke ontwikkel. Verhogings van GOT tot meer as vyf keer die boonste limiet van die normale omvang is waargeneem by 4 % van alle pasiënte wat met 600 mg efavirens behandel is, en by 10 % van die pasiënte wat seropositief is vir Hepatitis B of C. By pasiënte wat met kontrole behandel is. Die voorkoms van GOT-verhogings tot op hierdie vlak was 1,5 tot 2 %, ongeag die serologie van Hepatitis B of C. Geïsoleerde verhogings van GOT by pasiënte wat efavirens ontvang, kan die induksie van ensiem weerspieël wat nie verband hou met lewertoksisiteit nie.
Lipiede: 'n Verhoging van die totale cholesterol van 10 tot 20 % is waargeneem by sommige onbesmette vrywilligers wat efavirens ontvang. Verhogings in nie-vastende totale cholesterol en HDL van onderskeidelik ongeveer 20 % en 25 % is waargeneem by pasiënte wat met efavirens + SDV + 3TC behandel is en van ongeveer 40 % en 35 % by pasiënte wat met efavirens + IDV behandel is. Die effekte van efavirens op trigliseriede en LDL was nie goed gekenmerk nie. Die kliniese belang van hierdie bevindings is onbekend.
Indien u enige newe-effekte waarneem wat nie in hierdie biljet genoem word nie, lig u dokter of apteker in.

6. BERGING EN WEGDOENING VAN ERIGE CAPSULES
Bêre by of onder 30 ° C. Beskerm teen lig. Hou die houer dig toe.
HOU ALLE MEDISYNE BUITE BEREIK VAN KINDERS.
Neem alle ongebruikte medisyne na u apteker.
Moenie van ongebruikte medisyne in dreine of rioolstelsels (bv. toilette) wegdoen nie.

7. AANBIEDING VAN ERIGE CAPSULES
ERIGE 50 mg CAPSULES:
Kapsules word verpak in 'n wit, ronde 40 ml swaargewig HDPE-houer met 'n 33 mm PP-sluiting met 'n induksie-seëlprop.
Geen droogmiddel is in die houer ingesluit nie.
Pakgrootte: 30's: Een HDPE-houer met 30 kapsules.

ERIGE 100 mg CAPSULES:
Kapsules word verpak in 'n wit, ronde 40 ml swaargewig HDPE-houer met 'n 33 mm PP-sluiting met 'n induksie-seëlprop.
Geen droogmiddel is in die houer ingesluit nie.
Pakgrootte: 30's: Een HDPE-houer met 30 kapsules.

ERIGE 200 mg CAPSULES:
1. Die kapsules word verpak in 'n wit, ronde 70 ml HDPE-houer met 'n 43 mm PP-afsluiting met 'n induksie-seëlprop.

Geen droogmiddel is in die houer ingesluit nie.
Pakgrootte: 30's: Een HDPE-houer met 30 kapsules.

2. Die kapsules word verpak in 'n wit, ronde 200 ml swaargewig HDPE-houer met 'n 45 mm PP-sluiting met 'n induksie-seëlprop.

Geen droogmiddel is in die houer ingesluit nie.
Pakgrootte: 90's: Een HDPE-houer met 90 kapsules.

8. IDENTIFIKASIE VAN ERIGE CAPSULES
ERIGE 50 mg CAPSULES:
Geel/wit grootte '4' harde gelatienkapsules met 'D' op 'n geel dop en '72' op 'n wit liggaam gedruk met swart eetbare ink, en gevul met wit tot naaswit poeier.
ERIGE 100 mg CAPSULES:
Wit/wit grootte '2' harde gelatienkapsules met 'D' op 'n wit dop en '71' op 'n wit liggaam gedruk met swart eetbare ink, en gevul met wit tot naaswit poeier.
ERIGE 200 mg CAPSULES:
Geel/geel grootte 'OEL' harde gelatienkapsules met 'D' op 'n geel dop en '36' op 'n geel liggaam gedruk met swart eetbare ink, en gevul met wit tot naaswit poeier.

9. REGISTRASIENOMMER
ERIGE 50 mg CAPSULES:
SUID-AFRIKA: 41/20.2.8/0541

ERIGE 100 mg CAPSULES:
SUID-AFRIKA: 41/20.2.8/0542

ERIGE 200 mg CAPSULES:
SUID-AFRIKA: 41/20.2.8/0543

10. NAAM EN ADRES VAN REGISTRASIEHOUER
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