ERIGE TABLETS P1522658

ERIGE TABLETS P1522658

NOVAGEN® Pharma

PROFESSIONAL INFORMATION

SCHEDULING STATUS:
SOUTH AFRICA: S4

PROPRIETARY NAME AND DOSAGE FORM:
ERIGE 600 mg TABLETS (Tablet)

COMPOSITION:
ERIGE 600 mg TABLETS:
Each film-coated tablet contains 600 mg efavirenz.
Excipients: Microcrystalline cellulose, sodium lauryl sulphate, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, Opadry Yellow (Hypromellose, titanium dioxide, iron oxide yellow and PEG 400).
ERIGE 600 mg TABLETS contains lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:
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.

Pharmacodynamic properties:
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 μM. 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).
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 600 mg TABLETS, 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 600 mg TABLETS is contraindicated in patients with hypersensitivity to **ERIGE 600 mg TABLETS** or any of it components.
ERIGE 600 mg TABLETS 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 600 mg TABLETS (see "**CONTRAINDICATIONS**").
Resistant virus emerges rapidly when **ERIGE 600 mg TABLETS** is administered as monotherapy, therefore, **ERIGE 600 mg TABLETS** 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 600 mg TABLETS**, 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.
Skin Rash: Mild to-moderate rash has been reported with **ERIGE 600 mg TABLETS** use and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. **ERIGE 600 mg TABLETS** should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** in children may be considered.

Nervous System Symptoms: Nervous system symptoms have been reported with **ERIGE 600 mg TABLETS** 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 600 mg TABLETS**-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 600 mg TABLETS** may be required.

Special Populations: Because of the extensive cytochrome P450-mediated metabolism of **ERIGE 600 mg TABLETS** limited clinical experience in patients with chronic liver disease, caution should be exercised in administering **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS** (see "**SIDE EFFECTS**").

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.

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 600 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 **ERIGE 600 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:
ERIGE 600 mg TABLETS has not been studied in paediatric patients below 3 years of age or who weigh less than 40 kg. Therefore, **ERIGE 600 mg TABLETS** is not recommended in this group.

Effects on ability to drive and use machines:
ERIGE 600 mg TABLETS 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.

INTERACTIONS:
ERIGE 600 mg TABLETS is an inducer of CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with **ERIGE 600 mg TABLETS**.
Indinavir: When indinavir (800 mg every 6 hours) was given with **ERIGE 600 mg TABLETS** (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 600 mg TABLETS** and indinavir are co-administered. No adjustment of the dose of **ERIGE 600 mg TABLETS** is necessary when given with indinavir.

Ritonavir: When **ERIGE 600 mg TABLETS** (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, paraesthesia and elevated liver enzymes occurred). Monitoring of liver enzymes is recommended when **ERIGE 600 mg TABLETS** is used in combination with ritonavir.

Saquinavir: When saquinavir (1200 mg given 3 times a day, soft capsule formulation) was given with **ERIGE 600 mg TABLETS** the saquinavir AUC and C_{max} were decreased by 62 % and 50 % respectively. Use of **ERIGE 600 mg TABLETS** in combination with saquinavir as the sole PI is not recommended.

Rifamycins: Rifampicin reduced **ERIGE 600 mg TABLETS** AUC by 26 % and C_{max} by 20 % in 12 uninfected volunteers. The dose of **ERIGE 600 mg TABLETS** must be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with **ERIGE 600 mg TABLETS**. Rifabutin has not been studied in combination with **ERIGE 600 mg TABLETS. Clarithromycin:** Co-administration of 400 mg of **ERIGE 600 mg TABLETS** 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 600 mg TABLETS**. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46 % developed rash while receiving **ERIGE 600 mg TABLETS** and clarithromycin. No dose adjustment of **ERIGE 600 mg TABLETS** 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 600 mg TABLETS**. 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 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS**. 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 600 mg TABLETS does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received **ERIGE 600 mg TABLETS**. 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:
The use of **ERIGE 600 mg TABLETS** during pregnancy is not recommended, as teratogenicity has been noted. Malformations have been observed in foetuses from **ERIGE 600 mg TABLETS**-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 600 mg TABLETS**.
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 600 mg TABLETS** (see "**CONTRAINDICATIONS**").

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 600 mg TABLETS** do not breastfeed their infants. It is recommended that HIV-infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

DOSAGE AND DIRECTIONS FOR USE:
Adults: The recommended dosage of **ERIGE 600 mg TABLETS** in combination with a protease inhibitor, and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily. **ERIGE 600 mg TABLETS** 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 600 mg TABLETS must be given in combination with other antiretroviral medications (see "**INTERACTIONS**").
Adolescents and children (17 years and under): ERIGE 600 mg TABLETS may be taken on an empty stomach, at bedtime. **ERIGE 600 mg TABLETS** can only be used in adults and children who weigh greater than or equal to 40 kg.

SIDE EFFECTS:
ERIGE 600 mg TABLETS can have 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 600 mg TABLETS**. Similar elevations were seen in patients treated with control regimens. In 156 patients treated with 600 mg of **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS**. 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 600 mg TABLETS** +IDV. The effects of **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS**. Since **ERIGE 600 mg TABLETS** is highly protein bound, dialysis is unlikely to significantly remove the drug from blood.

IDENTIFICATION:
Yellow coloured oval biconvex film-coated tablets debossed with 'D' on one side and '37' on the other side.

PRESENTATION:
Tablets are packed in milky white round 80 ml HDPE containers with screw type polypropylene closure with induction sealing wad.
Pack size: 30 tablets per HDPE container.

STORAGE INSTRUCTIONS:
Store at or below 30 °C.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
SOUTH AFRICA: A40/20.2.8/0513

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 600 mg TABLETS (Tablet).
Efavirenz.

Read all of this leaflet carefully before you start taking ERIGE 600 mg TABLETS
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist
- **ERIGE 600 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 ERIGE 600 mg TABLETS CONTAINS:
- The active substance is efavirenz. Each film-coated tablet contains 600 mg efavirenz.
- The other ingredients are: Croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, opadry yellow and sodium lauryl sulfate.
- Contains sugar (lactose monohydrate).

2. WHAT ERIGE 600 mg TABLETS IS USED FOR:
ERIGE 600 mg TABLETS 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 600 mg TABLETS:
Do not take ERIGE 600 mg TABLETS:
- If you are hypersensitive to efavirenz or any ingredient of the formulation
- If you are using terfenadine astemizole, cisapride, midazolam, trizolam or ergot derivatives. This can create the potential for serious and/or life-threatening adverse events (eg. cardiac arrhythmias, prolonged sedation or respiratory depression).

Take special care with ERIGE 600 mg TABLETS:
- **ERIGE 600 mg TABLETS** 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 healthcare professional for advice.
- Monitoring of cholesterol should be considered in patients treated with efavirenz.
- You may develop a condition known as lipodystrophy while taking **ERIGE 600 mg TABLETS**. Inform your doctor or healthcare professional if you notice a change in the distribution of your body fat (e.g. accumulation of fat around the waist/stomach area, on the back of the neck and between the shoulders (buffalo hump), breast enlargement), wasting of the arms, legs and facial muscles, and increased blood glucose and lipid values.
- If you are taking **ERIGE 600 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 **ERIGE 600 mg TABLETS**. Your doctor will treat the infections appropriately.
- You may develop a condition known as osteonecrosis while taking **ERIGE 600 mg TABLETS**. Seek medical advice if you experience joint aches and pain, joint stiffness or difficulty in movement.
- You may continue to develop opportunistic infections and other complications of HIV infection while taking **ERIGE 600 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 **ERIGE 600 mg TABLETS**. Appropriate precautions should continue to be employed.

Pregnancy and Breastfeeding:
Safety of **ERIGE 600 mg TABLETS** 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 breastfeed their infants under any circumstances in order to avoid transmission of HIV.

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice before taking **ERIGE 600 mg TABLETS**.

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

Important information about some of the ingredients of ERIGE 600 mg TABLETS:
ERIGE 600 mg TABLETS contains lactose (milk sugar). If you know you are unable to digest and metabolize lactose (i.e lactose intolerance), tell your doctor before taking **ERIGE 600 mg TABLETS**.

Taking other medicines with ERIGE 600 mg TABLETS:
Always tell your healthcare professional if you are taking any other medicine.
(This includes complementary or traditional medicines.)
ERIGE 600 mg TABLETS interacts with indinavir, ritonavir, saquinavir, rifampicin, clarithromycin, oral contraceptives, methadone and St. John's Wort.

4. HOW TO TAKE ERIGE 600 mg TABLETS:
Do not share medicines prescribed for you with any other person.
Always take **ERIGE 600 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 **ERIGE 600 mg TABLETS** is too strong or too weak, talk to 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 600 mg TABLETS must be given in combination with other antiretroviral medications (see **Taking other medicines with ERIGE 600 mg TABLETS**).

Adolescents and children (17 years and under):
ERIGE 600 mg TABLETS may be taken with or without food, as desired. **ERIGE 600 mg TABLETS** can only be used in adults and children who weigh greater than or equal to 40 kg.

If you take more ERIGE 600 mg TABLETS 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 ERIGE 600 mg TABLETS:
Do not take a double dose to make up for forgotten individual doses.

5. POSSIBLE SIDE EFFECTS:
ERIGE 600 mg TABLETS can have side effects.
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 (8,0%), 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 600 mg 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 behavior, 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 600 mg TABLETS** should be altered to the potential for additive central nervous system effects when **ERIGE 600 mg TABLETS** is used concomitantly with alcohol or psychoactive drugs.

Patients should be informed that **ERIGE 600 mg TABLETS** 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:

General disorders and administrative site conditions:
Alcohol intolerance, allergic reaction, asthenia, hot flushes, influenza-like symptoms, malaise, pain and syncope.

Gastrointestinal disorders:
Gastritis, gastroenteritis and gastroesophageal reflux, taste perversion.

Ear and labyrinth disorders:
Tinnitus.

Cardiac disorders:
Blushing, palpitations and tachycardia.

Hepato-biliary disorders:
Hepatitis.

Metabolism and nutrition disorders:
Weight gain and weight loss.

Musculoskeletal, connective tissue and bone disorders:
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, thoracic and mediastinal disorders:
Asthma, sinusitis and upper respiratory tract infections.

Skin and subcutaneous tissue disorders:
Acne, alopecia, eczema, folliculitis, seborrhea, skin exfoliation and urticaria.

Eye disorders:
Abnormal vision.

Investigations:
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 is unknown.

Not all side effects reported for **ERIGE 600 mg TABLETS** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **ERIGE 600 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 ERIGE 600 mg TABLETS:
Store at or below 30 °C
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 600 mg TABLETS:
Tablets are packed in milky white round 80 ml HDPE containers with screw type polypropylene closure with induction sealing wad.
Pack size: 30 tablets per HDPE container.

8. IDENTIFICATION OF ERIGE 600 mg TABLETS:
Yellow coloured oval biconvex film-coated tablets debossed with 'D' on one side and '37' on the other side.

9. REGISTRATION NUMBER:
SOUTH AFRICA: A40/20.2.8/0513

12. NAME AND ADDRESS OF REGISTRATION NUMBER:
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NOVAGEN® Pharma

SKEDULERINGSTATUS:
SUID-AFRIKA: S4

EIENDOMSNAAM EN DOSERINGSVORM:
ERIGE 600 mg TABLETS (tablet)

SAMESTELLING:

ERIGE 600 mg TABLETS:

Elke filmbedekte tablet bevat 600 mg efavirens.

Eksipiënte: Mikrokristallyne sellulose, natriumlaurielsulfaat, natriumkroskarmellose, hidroksipropiel sellulose, laktosemonohidraat, magnesiumstearaat, Opadry geel (Hipromellose, titaandioksied, ysteroksiedgeel en PEG 400).

ERIGE 600 mg TABLETS bevat laktosemonohidraat.

FARMAKOLOGESE KLASSIFIKASIE:

A 20.2.8 Virusteenmiddels

FARMAKOLOGIESE WERKING

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.

Farmakodinamiese eienskappe

***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.

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. Die mutasie by die RT aminosuur posisie 103 (lisien tot asparagiene), was die mees dikwels waargeneem (groter of gelyk aan 90 %). 'n Gemiddelde verlies in vatbaarheid (IK_{90}) teenoor efavirenz van 47 voudig was waargeneem in 26 kliniese isolators.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 isolator in vergelyking met basislyn waargeneem. Al vyf isolate 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, 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 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 farmakokinetika van efavirens is nie voldoende in pasiënte met belemmerde lewerfunksie bestudeer nie.

Belemmerde nierfunsie:

Die farmakokinetika van efavirens is nie in pasiente met belemmerde nierfunksie bestudeer 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 farmakokinetika van efavirens soortgelyk in mans en vroue, asook onder verskillende rasgroepe is.

Geriatriese gebruik:

Farmakokinetika van efavirens is nie bestudeer in mense van 65 jaar en ouer nie, om te sien of hulle verskillend reageer.

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 600 mg TABLETS 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/of 3 jaar en ouer is.

KONTRA-INDIKASIES:

ERIGE 600 mg TABLETS word teenaangedui in pasiënte met 'n hipersensitiwiteit teen **ERIGE 600 mg TABLETS** of enige van sy komponente.

ERIGE 600 mg TABLETS 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 600 mg TABLETS geneem moet word nie (sien **"KONTRA-INDIKASIES" en "NEWE-EFFEKTE").**

Weerstandige virus stamme ontwikkel vinnig wanneer **ERIGE 600 mg TABLETS** as monoterapie toegedien word. Daarom behoort **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** 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.

Veluitslag: Min tot matige uitslag is gerapporteer met gebruik van **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** moet gestaak word by pasiënte wat ernstige uitslag ontwikkel wat verband hou met blase, afskilfering, mukosale betrokkenheid of koors. As die behandeling met **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** by kinders oorweeg word.

Simptome van Senuweestelsel: Simptome van die senuweestelsel is aangemeld met gebruik van **ERIGE 600 mg TABLETS** (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 600 mg TABLETS**-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 600 mg TABLETS** nodig mag wees.

Spesiale Bevolkings: Vanweë die uitgebreide sitochroom P450-gemedieërde metabolisme van **ERIGE 600 mg TABLETS** beperkte kliniese ondervinding by pasiënte met chroniese lewersiekte, moet versigtigheid toegepas word by die toediening van **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS** behandel word (sien **"NEWE-EFFEKTE"**).

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.

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.

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 600 mg TABLETS** 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 600 mg TABLETS**, 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.

Pediatriese gebruik:

ERIGE 600 mg TABLETS is nie bestudeer by kinders onder 3 jaar nie, of wat minder as 40 kg weeg nie. Daarom word **ERIGE 600 mg TABLETS** nie in hierdie groep aanbeveel nie.

Effekte op die bestuur en bestuur van masjiene:

ERIGE 600 mg TABLETS 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 600 mg TABLETS is 'n induseerder van CYP3A4. Ander verbindings wat 'n substraat van CYP3A4 is, mag laer plamakonsentrasies hê wanneer dit saam met **ERIGE 600 mg TABLETS** toegedien word.

Indinavir: Wanneer indinavir (800 mg elke 8 ure) saam met **ERIGE 600 mg TABLETS** (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 600 mg TABLETS** is nodig wanneer dit saam met indinavir toegedien word nie.

Ritonavir: Toe **ERIGE 600 mg TABLETS** (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 600 mg TABLETS** in kombinasie met ritonavir gebruik word.

Sakinavir: Toe sakinavir (1 200mg, sagte kapsuleformulasie, 3 keer per dag) saam met **ERIGE 600 mg TABLETS** toegedien is, het die sakinavir AOK en K_{maks} met 62 % en 50 % respektiewelik afgeneem. Die gebruik van **ERIGE 600 mg TABLETS** in kombinasie met sakinavir as die enigste PI word nie aanbeveel nie.

Rifamisiene: Rifampisien het die AOK van **ERIGE 600 mg TABLETS** met 26 % en die K_{maks} met 20 % in 12 onbesmette vrywilligers laat afneem. Die **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** gebruik word nie. Rifabutien is nie in kombinasie met **ERIGE 600 mg TABLETS** bestudeer nie.

Klaritromisien: Die medetoediening van 400 mg **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS** en klaritomisien ontvang het. Geen dosisaanpassings van **ERIGE 600 mg TABLETS** 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 600 mg TABLETS**. 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 600 mg TABLETS** 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 600 mg TABLETS** met metadoon in MIV-besmette IV dwelmgebruikers, 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 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS bind nie aan kannabinoïedreseptore nie. Vals positiewe urienkannabinoïed toetsresultate is in onbesmette vrywilligers wat **ERIGE 600 mg TABLETS** 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:

Die gebruik van **ERIGE 600 mg TABLETS** word nie gedurende swangerskap en laktasie aanbeveel nie, aangesien teratogenisiteit opgemerk is. Wanvorming is waargeneem in fetusse van **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** ontvang.

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 600 mg TABLETS** te ondergaan (sien: **"KONTRA-INDIKASIES"**).

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 600 mg TABLETS** 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 600 mg TABLETS** dosis in kombinasie met 'n proteaseïnhibeerder, en/of nukleosied analoogtrutranskripaseïnhibeerders (NTTI's) is 600 mg een keer per dag. **ERIGE 600 mg TABLETS** 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 600 mg TABLETS moet in kombinasie met ander anti-retro virus middels toegedien word (sien **"INTERAKSIES"**).

Adolessente en kinders (jonger as 17 jaar): ERIGE 600 mg TABLETS mag geneem word op n leë maag, teen slapenstyd. **ERIGE 600 mg TABLETS** behoort slegs in volwassenes en kinders wat 40 kg of meer weeg, gebruik te word.

NEWE-EFFEKTE

ERIGE 600 mg TABLETS kan newe-effekte hê.

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, torakale- 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.

Muskuloskeletale, 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 pasïente met virale hepatitis. 'n Toename in serum cholesterol- en trigliseriedkonsentrasies is aangemeld.

Lewer ensieme: Toenames in AST en ALT na meer as vyf keer die boonste limiet van normaal is in pasiente wat met 600 mg **ERIGE 600 mg TABLETS** behandel is, waargeneem.

Soortgelyke verhogings is gesien by pasiënte wat met kontrole behandelings behandel is. In 156 pasiënte wat met 600 mg **ERIGE 600 mg TABLETS** 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 600 mg TABLETS** 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 600 mg TABLETS** ontvang, kan die induksie van ensiem weerspieël wat nie met lewertoksisiteit verband hou nie (sien **"WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS"**).

Lipiede: Toenames van 10 tot 20 % in totale cholesterol is in sommige onbesmette vrywilligers wat **ERIGE 600 mg TABLETS** ontvang het, waargeneem. Toenames in nie-vastende totale cholesterol en HDL van ongeveer 20 % tot 25 % respektiewelik, is in pasiente wat met efavirens + ZDV +3TC behandel is, waargeneem en van ongeveer 40 % tot 35 % in pasïente wat met **ERIGE 600 mg TABLETS** + IDV behandel is. Die effek van **ERIGE 600 mg TABLETS** 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 pasïente 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 600 mg TABLETS** behoort uit algemene ondersteunende maatreëls, insluitend die monitering van lewenstekens en observasie van die pasïent 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 600 mg TABLETS** nie. Aangesien **ERIGE 600 mg TABLETS** hoogs proteïengebonde is, is dit onwaarskynlik dat die middel tot enige noemenswaardige mate deur dialise uit die bloed verwyder word.

IDENTIFIKASIE:

Geelkleurige ovaal, bikonvekse filmbedekte tablette gebosselleer met 'D' aan die een kant en '37' aan die ander kant.

AANBIEDING:

Die tablette word verpak in wit, ronde 80 ml HDPE-houers met polipropileen-skroefsluitings met 'n induksie-seëlprop.

Pakgrootte: 30 tablette per HDPE-houer.

BEWARINGSINSTRUKSIES:

Bewaar teen of benede 30 °C.

HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:

SUID-AFRIKA: A40/20.2.8/0513

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:

Novagen Pharma (Pty) Ltd
Kantoor 2, Sovereignrylaan 100
Route 21 Corporate Park
Nellmapiusrylaan
Irene - Pretoria
Suid-Afrika

DATUM VAN PUBLIKASIE VAN HIERDIE PROFESSIONELE INLIGTING:

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P1522658

⬆DETACH BEFORE DISPENSING

PASIËNTINLIGTINGSBILJET

SKEDULERINGSTATUS
SUID-AFRIKA: S4

EIENDOMSNAAM, STERKTE EN FARMASEUTIESE VORM
ERIGE 600 mg TABLETS (Tablet)
Efavirens.

Lees die hele biljet sorgvuldig deur voordat u met ERIGE 600 mg TABLETS begin

- Bewaar hierdie biljet. Miskien moet u dit weer lees.
- Vra u dokter of apteker as u nog vrae het.
- **ERIGE 600 mg TABLETS** 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 600 mg TABLETS BEVAT

- Die aktiewe bestanddeel is efavirens. Elke filmbedekte tablet bevat 600 mg efavirenz.
- Die ander bestanddele is: Natriumkroskarmellose, hidroksipropielsellulose, laktosemonohidraat, magnesiumstearaat, mikrokristallyne sellulose, opadry geel en natriumlaurielsulfaat.
- Bevat suiker (laktosemonohidraat).

2. WAT ERIGE 600 mg TABLETS VOOR GEBRUIK WORD

ERIGE 600 mg TABLETS 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 600 mg TABLETS NEEM

Moenie ERIGE 600 mg TABLETS neem:

- as u hipersensitief (allergies) vir efavirens of een van die ander bestanddele van die formulasie is
- 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 600 mg TABLETS:

- **ERIGE 600 mg TABLETS** moet nie as 'n enkele middel gebruik word om MIV te behandel nie, of as 'n enigste middel by 'n mislukte regimen gevoeg word. Raadpleeg u dokter, apteker of ander gesondheidsorgwerker vir advies.
- Monitering van cholesterol moet oorweeg word by pasiënte wat met efavirens behandel word.
- U kan 'n toestand wat bekend staan as lipodistrofie ontwikkel terwyl u **ERIGE 600 mg TABLETS** neem. Stel u dokter of gesondheidswerker in kennis indien u 'n verandering in die verspreiding van u liggaamsvet (bv. ophoping van vet rondom die middel/maagarea, op die agterkant van die nek en tussen die skouers (buffelskof), borsvergroting) sien, uittering van die arms, bene en gesigspiere, en verhoogde bloedglukose en lipiedwaardes.
- As u die eerste keer **ERIGE 600 mg TABLETS** neem, kan u binne die eerste maande van die behandeling 'n toestand met die naam Immuun Rekonstitusie Inflammatoriese Sindroom (IRIS) ontwikkel. Hierdie toestand kan veroorsaak dat opportunistiese infeksies wat behandel word erger word, of dat opportunistiese siektes wat asimptomaties was, ontmasker kan word. Vertel u dokter of gesondheidsorgwerker as u algemene gesondheid vererger of as u dink dat u 'n infeksie het. U moet nie ophou om **ERIGE 600 mg TABLETS** te neem nie. U dokter sal die infeksies toepaslik behandel.
- U kan 'n toestand ontwikkel wat bekend staan as osteonekrose terwyl u **ERIGE 600 mg TABLETS** neem. Kry mediese advies indien u gewrigspyn en pyn, gewrigstyfheid of probleme met beweging ervaar.
- U kan voortgaan om opportunistiese infeksies en ander komplikasies van MIV-infeksie te ontwikkel terwyl u **ERIGE 600 mg TABLETS** neem. U moet noukeurig dopgehou word deur professionele persone in die gesondheidsorg wat ervare is in die behandeling van pasiënte met gepaardgaande MIV-siekte. Gereelde monitering van viruslading en CD4-tellings moet gedoen word.
- U loop nog steeds die risiko om MIV aan ander oor te dra deur seksuele kontak of bloedbesmetting terwyl u antiretrovirale terapie ondergaan, insluitend **ERIGE 600 mg TABLETS**. Daar moet voortgegaan word om toepaslike voorsorgmaatreëls te tref.

Swangerskap en borsvoeding:

Die veiligheid van **ERIGE 600 mg TABLETS** by swanger en lakterende vroue is nie vasgestel nie. Vroue wat swangerskap potensiaal het, 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 om MIV-oordrag te voorkom nie.

As u swanger is of u baba borsvoed, raadpleeg u dokter, apteker of ander professionele gesondheidsorgwerker voordat u **ERIGE 600 mg TABLETS** neem.

Bestuur en gebruik van masjinerie:

Moet nie bestuur of masjinerie gebruik as u slaperig, lomerig is of voel dat u konsentrasie nie meer goed is nie.

Belangrike inligting oor sommige van die bestanddele van ERIGE 600 mg TABLETS:

ERIGE 600 mg TABLETS bevat laktose (melksuiker). Indien u weet dat u nie laktose kan verteer en metaboliseer nie (m.a.w. laktose-intoleransie), vertel u dokter voordat u **ERIGE 600 mg TABLETS** neem.

Neem van ander medisyne saam met ERIGE 600 mg TABLETS

Vertel altyd u gesondheidswerker as u enige ander medisyne neem (dit sluit komplementêre of tradisionele medisyne in).

ERIGE 600 mg TABLETS is in interaksie met indinavir, ritonavir, sakwinavir, rifampisien, klaritromisien, orale voorbehoedmiddels, metadoon en St. Johns-wort.

4. HOE OM ERIGE 600 mg TABLETS TE NEEM

Moenie medisyne wat vir u voorgeskryf is, met enige ander persoon deel nie.

Neem altyd **ERIGE 600 mg TABLETS** presies soos deur u dokter opdrag gegee het. U moet dit met u dokter of apteker nagaan as u onseker is.

Vertel u dokter of apteker as u die indruk het dat die effek van **ERIGE 600 mg TABLETS** 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 600 mg TABLETS moet gegee word in kombinasie met ander antiretrovirale medisyne (sien **Gebruik van ander medisyne saam met ERIGE 600 mg TABLETS**).

Adolessente en kinders (17 jaar en jonger):

ERIGE 600 mg TABLETS kan geneem word met of sonder voedsel na wense. **ERIGE 600 mg TABLETS** kan slegs gebruik word by volwassenes en kinders wat 40 kg en meer weeg.

As u meer **ERIGE 600 mg TABLETS** neem as wat u behoort:

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 ERIGE 600 mg TABLETS te neem:

Moenie 'n dubbele dosis neem om op te maak vir die vergete dosis nie.

5. MOONTLIKE NEWE-EFFEKTE

ERIGE 600 mg TABLETS kan newe-effekte hê.

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 uitslag 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 waarneming 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 hoër grade 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 is 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 600 mg TABLETS** ontvang, moet verander word vir die potensiële addisionele sentrale senuweestelsel gevolge wanneer **ERIGE 600 mg TABLETS** tesame met alkohol of psigo-aktiewe middels gebruik word.

Pasiënte moet in kennis gestel word dat **ERIGE 600 mg TABLETS** 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:

Algemene afwykings en toedieningsplek kondisies:

Alkoholverdraagsaamheid, allergiese reaksie, astenie, warm gloede, griepagtige simptome, malaise, pyn en sinkopee.

Maag:

Gastritis, gastroënteritis en gastro-esofageale refluks, smaakafwyking.

Oor en labirint afwykings:

Tinnitus.

Hartafwykings:

Blosing, hartkloppings en tagikardie.

Lewer- en galafwykings:

Geelsug.

Metaboliese en Voedingsafwykings:

Gewigstoename en gewigsverlies.

Muskuloskeletale, bindweefsel en beenafwykings:

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 .

Respiratoriese, torakale en medistinale afwykings:

Asma, sinusitis en infeksies in die boonste lugweg.

Vel en subkutane weefselafwykings:

Aknee, alopesie, ekseem, follikulitis, seborree, velafskilfering en urtikarie.

Oogafwykings:

Abnormale sig.

Ondersoeke:

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 ontwikkel. 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 en van ongeveer 40 % en 35 % behandel is, 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.

Nie alle newe-effekte wat gerapporteer is vir **ERIGE 600 mg TABLETS** is ingesluit in die biljet nie. Sou u algemene gesondheid agteruitgaan of u enige ongewenste gebeure ervaar terwyl u **ERIGE 600 mg TABLETS** gebruik, moet u u dokter, apteker of ander gesondheidsorg professioneel vir advies nader.

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 600 mg TABLETS

Bêre by of onder 30 ° C.

HOU ALLE MEDISYNE BUITE BEREIK VAN KINDERS.

Neem alle ongebruikte medisyne na u apteker.

Moenie ongebruikte medisyne in dreine of rioolstelsels (bv. toilette) wegdoen nie.

7. AANBIEDING VAN ERIGE 600 mg TABLETS

Tablette word verpak in wit, ronde 80 ml HDPE-houers met skroeftipe polipropileen sluitings met induksie-seëlprop.

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

8. IDENTIFIKASIE VAN ERIGE 600 mg TABLETS

Geel ovale bikonvekse filmbedekte tablette gebosselleer met 'D' aan die een kant en '37' aan die ander kant.

9. REGISTRASIENOMMER

SUID-AFRIKA: 41/20.2.8/0513

10. NAAM EN ADRES VAN REGISTRASIEHOUER

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11. DATUM VAN PUBLIKASIE

Datum van registrasie: 30 November 2007
Datum van die nuutste hersiening van die teks soos deur die Raad goedgekeur: 30 November 2007
Datum van kennisgewing met betrekking tot gewysigde Reg. 9 en 10: 02 Februarie 2015.

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