- **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.
- **SPECIAL POPULATIONS**
  - ***Liver disease:*** Efavirenz is contraindicated in patients with severe hepatic impairment and not recommended in patients with moderate hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild hepatic impairment. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals.
    The safety and efficacy of efavirenz has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse reactions. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered.
    In patients treated with other medicinal products associated with liver toxicity, monitoring of liver enzymes is also recommended. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.
  - ***Renal insufficiency:*** There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.
  - ***Elderly patients:*** Insufficient numbers of elderly patients have been evaluated to determine whether they respond differently than younger patients.
  - ***Paediatric population:*** Efavirenz has not been evaluated in children below 3 months of age or who weigh less than 3.5 kg. Therefore, efavirenz should not be given to children less than 3 months of age. Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg. Rash was reported in children treated with efavirenz. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.
  - ***Lactose:*** Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

PREGNANCY AND LACTATION

Women of childbearing potential: Efavirenz should not be used during pregnancy, unless the patient's clinical condition requires such treatment. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.

Contraception in males and females:
Barrier contraception should always be used in combination with other methods of contraception. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended.

Pregnancy: As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes are sealed), this potential risk would concern women exposed to efavirenz during the first trimester of pregnancy.

Breast-feeding: Efavirenz has been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz in newborns/infants. Risk to the infant cannot be excluded. Breast-feeding should be discontinued during treatment with efavirenz. It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

DRUG INTERACTIONS

Efavirenz is an *in vivo* inducer of CYP3A4, CYP2B6 and UGT1A1. Compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with efavirenz. *In vitro* efavirenz is also an inhibitor of CYP3A4. Theoretically, efavirenz may therefore initially increase the exposure to CYP3A4 substrates and caution is warranted for CYP3A4 substrates with narrow therapeutic index. Efavirenz may be an inducer of CYP2C19 and CYP2C9; however, inhibition has also been observed *in vitro* and the net effect of co-administration with substrates of these enzymes is not clear.

Efavirenz exposure may be increased when given with medicinal products (for example, ritonavir) or food (for example, grapefruit juice), which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example Ginkgo biloba extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated. Concomitant use of Ginkgo biloba extracts is not recommended.

Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events.

MAIN SIDE/ADVERSE EFFECTS

Adverse reactions are listed by system organ class and ranked by frequency: Very Common, Common, Uncommon, Rare, Very Rare and not known.

- **Immune System Disorders**
  Uncommon: hypersensitivity
- **Metabolism and Nutrition Disorders**
  Common: hypertriglyceridaemia
  Uncommon: hypercholesterolaemia
- **Psychiatric Disorders**
  Common: abnormal dreams, anxiety, depression, insomnia
  Uncommon: affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis, suicide attempt, suicide ideation
  Rare: delusion, neurosis, completed suicide
- **Nervous System Disorders**
  Common: cerebellar coordination and balance disturbances, disturbance in attention, dizziness, headache, somnolence
  Uncommon: agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal, tremor
- **Eye Disorders**
  Uncommon: vision blurred
- **Ear and Labyrinth Disorders**
  Uncommon: tinnitus, vetigo
- **Vascular Disorders**
  Uncommon: flushing
- **Gastrointestinal Disorders**
  Common: abdominal pain, diarrhoea, nausea, vomiting
  Uncommon: pancreatitis
- **Hepatobiliary Disorders**
  Common: aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, gamma-glutamyltransferase (GGT) increased
  Uncommon: hepatitis acute
  Rare: hepatic failure
- **Skin and Subcutaneous Tissue Disorders**
  Very common: rash
  Common: pruritus
  Uncommon: erythema multiforme, Stevens-Johnson syndrome
  Rare: photoallergic dermatitis
- **Reproductive System and Breast Disorders**
  Uncommon: gynaecomastia
- **General Disorders and Administration Site Conditions**
  Common: fatigue

OVERDOSE AND TREATMENT

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms.

Treatment of overdose with efavirenz 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 efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood.

DOSAGE & ADMINISTRATION

Efavirenz must be given in combination with other antiretroviral medicines.
In order to improve the tolerability of nervous system adverse reactions, bedtime dosing is recommended.
Adults and adolescents over 40 kg: The recommended dose of efavirenz in combination with nucleoside analogue reverse transcriptase inhibitors (NRTIs) with or without a PI is 600 mg orally, once daily.
Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg.
Dose adjustment: If efavirenz is coadministered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the efavirenz dose must be reduced by 50%, i.e., to 300 mg once daily. When treatment with voriconazole is stopped, the initial dose of efavirenz should be restored. If efavirenz is coadministered with rifampicin to patients weighing 50 kg or more, an increase in the dose of efavirenz to 800 mg/day may be considered.

SPECIAL POPULATIONS

Renal impairment: The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.
Hepatic impairment: Patients with mild liver disease may be treated with their normally recommended dose of efavirenz. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms.
Paediatric population: The safety and efficacy of efavirenz in children below the age of 3 months or weighing less than 3.5 kg have not been established. No data are available.

METHOD OF ADMINISTRATION

It is recommended that efavirenz be taken on an empty stomach. The increased efavirenz concentrations observed following administration of efavirenz with food may lead to an increase in frequency of adverse reactions.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 30°C.
Protect from moisture and light.

Presentation/ Packing: Bottle pack of 30's

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Manufactured by: HOVID Bhd.
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