Nervous system symptoms
Dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking and depersonalization.

Psychiatric symptoms
Severe depression, suicidal ideation, non-fatal suicide attempts, aggressive behaviour, paranoid reactions and manic reactions. Depression, anxiety and nervousness have also been observed.

Skin rash
Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz. In most patients, rash resolves with continuing efavirenz therapy within one month. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids may be considered when efavirenz is restarted. Efavirenz should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Rash is more common and more severe in paediatric patients.

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 of these patients discontinued because of rash.

A few cases of pancreatitis have been described, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients. Additional post-marketing surveillance data reveal the following side effects:

Body as a Whole: allergic reactions, asthenia, redistribution/accumulation of body fat.
Central and Peripheral Nervous System: abnormal coordination, ataxia, convulsions, hypoesthesia, paresthesia, neuropathy, and tremor.
Endocrine: gynecomastia
Gastrointestinal: constipation, malabsorption
Cardiovascular: flushing, palpitations

Liver and Biliary System: hepatic enzyme increase, hepatic failure, hepatitis
Metabolic and Nutritional: hypercholesterolemia, hypertriglyceridemia
Musculoskeletal: arthralgia, myalgia, myopathy
Psychiatric: aggressive reactions, agitation, delusions, emotional lability, mania, neurosis, paranoia, psychosis, suicide
Respiratory: dyspnea
Skin and Appendages: erythema multiforme, nail disorders, skin discoloration, Stevens-Johnson Syndrome.
Special Senses: abnormal vision, tinnitus
Laboratory abnormalities
Liver enzymes: Among 1008 patients treated with 600 mg efavirenz in controlled clinical trials, 3% developed AST levels and 3% developed ALT levels greater than five times the upper limit of normal. Similar elevations of AST and ALT were seen in patients treated with control regimens.

Liver function tests should be monitored in patients with prior history of hepatitis B and/or C. Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity.

Lipids: Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving efavirenz. In patients treated with efavirenz + zidovudine + lamivudine, increases in non-fasting total cholesterol and HDL of approximately 20% and 25% respectively were observed. In patients treated with efavirenz + indinavir, increases in non-fasting cholesterol and HDL of approximately 40% and 35% respectively, were observed. The effects of efavirenz on triglycerides and LDL were not well-characterized since samples were taken from non-fasting patients. The clinical significance of these findings is unknown.

Serum amylase: Asymptomatic elevations in serum amylase greater than 1.5 times the upper limit of normal were seen in 10% of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown.

Cannabinoid test interaction: Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz.

Overdosage
Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

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 significantly remove the drug from blood.

Storage: Store below 25°C away from moisture

Presentation
Efavir – 600 Container of 30 tablets

Cipla

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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Efavirenz Tablets

EFAVIR-600

Composition
Efavir – 600
Each film-coated tablet contains
Efavirenz ..... 600 mg
Colours: Yellow Oxide of Iron & Titanium Dioxide

Description
Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase and does not significantly inhibit HIV-2 reverse transcriptase or cellular DNA polymerases α, β, γ or δ.

Indications
Efavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Dosage and Administration
Adults
The recommended dose of **Efavir** is 600 mg orally, once daily in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs).
It is recommended that **Efavir** be taken on an empty stomach, preferably at bedtime. The increased efavirenz concentrations observed following administration of **Efavir** with food may lead to an increase in frequency of adverse events. Dosing at bedtime may improve the tolerability of nervous system symptoms.

Contraindications
Efavir is contraindicated in patients with clinically significant hypersensitivity to any of its components.
Efavirenz must not be administered concurrently with astemizole, cisapride, midazolam, triazolam or ergot alkaloids because competition for the cytochrome P450 3A4 enzyme by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (for example, cardiac arrhythmias, prolonged sedation or respiratory depression).

Warnings and Precautions
ALERT: Find out about medicines that should not be taken with **Efavir**. (See "contraindications").
Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

Psychiatric symptoms
Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. These include severe depression, suicidal ideation/attempts, aggressive behaviour, paranoid reactions and manic reactions. Patients with a prior history of psychiatric disorders appear to be at greater risk for these psychiatric adverse experiences with the frequency of each of the above events ranging from 0.3% for manic reactions to 2% for both severe depression and suicidal ideation. There have also been occasional post-marketing reports of death by suicide, delusions and psychosis-like behaviour, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweigh the benefits.

Rash
Rash associated with blistering, moist desquamation or ulceration has been reported in clinical trials. The incidence of erythema multiforme or Stevens-Johnson Syndrome was approximately 0.1%. The median time to onset of rash in adults was 11 days and the median duration 16 days. The discontinuation rate for rash in clinical trials was 1.7% (17/1008). Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Nervous system symptoms
These include dizziness, insomnia, impaired concentration, somnolence, abnormal dreams and hallucinations. These symptoms were severe in 2% of patients and 2.1% of patients discontinued therapy as a result.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2-4 weeks. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms. Dosing at bedtime may improve the tolerability of these symptoms. Patients should be alerted to the potential for additive central nervous system effects when efavirenz is used concomitantly with alcohol or psychoactive drugs.

Patients who experience central nervous system symptoms such as dizziness, impaired concentration and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

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 normal, the benefit of continued therapy with efavirenz needs to be weighed against the unknown risks of significant liver toxicity.

Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution must be exercised in administering efavirenz to these patients.

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.

Cholesterol
Monitoring of cholesterol should be considered in patients treated with efavirenz.

Fat redistribution
Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Drug Interactions
Concomitant use of efavirenz and St. John's wort (*hypericum perforatum*) or St. John's wort-containing products is not recommended. Coadministration of NNRTIs, including efavirenz with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

Efavirenz is an inducer of CYP3A4 *in vivo*. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19 and 3A4 isoenzymes in the range of observed efavirenz concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isoenzymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs which induce CYP3A4 activity (e.g. Phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations. Drug interactions with efavirenz are summarized in the following table:

Table: Drugs That Should Not Be Coadministered with Efavirenz

Drug Class	Drugs Within Class Not to Be Coadministered with Efavirenz
Antihistamines	Astemizole
Benzodiazepines	Midazolam, triazolam
GI Motility Agents	Cisapride
Anti-Migraine	Ergot derivatives

Established Drug Interactions

Drug Name	*Effect*	*Clinical Comment*
Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Plasma concentrations decreased by efavirenz; clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of efavirenz is recommended when given with clarithromycin. Alternatives to clarithromycin, such as erythromycin should be considered (see "Other Drugs", below table). Other macrolide antibiotics, such as erythromycin, have not been studied in combination with efavirenz.
Indinavir	↓ indinavir concentration	Increase indinavir dose from 800 mg to 1000 mg every 8 hours.
Methadone	↓ methadone concentration	Coadministration in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. 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.
Ethinyl estradiol	↑ ethinyl estradiol concentration	Plasma concentrations increased by efavirenz; clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.
Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Rifampin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentrations unknown.
Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	Combination was associated with a higher frequency of adverse clinical experiences (e.g. dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when efavirenz is used in combination with ritonavir.
Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with efavirenz.

Other Potentially Clinically Significant Drug or Herbal Product Interactions with efavirenz

Anticoagulants: Warfarin	Plasma concentrations and effects potentially increased or decreased by efavirenz
Anticonvulsants: Phenytoin Phenobarbital Carbamazepine	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antifungals: Itraconazole Ketoconazole	Drug interaction studies with efavirenz and these imidazole and triazole antifungals have not been conducted. Efavirenz has the potential to decrease plasma concentrations of itraconazole and ketoconazole
Anti-HIV protease inhibitors Saquinavir/ritonavir combination	No pharmacokinetic data are available
Amprenavir	Efavirenz has the potential to decrease serum concentrations of amprenavir.
Non-nucleoside reverse transcriptase inhibitors	No studies have been performed with other NNRTIs.
St. John's wort (hypericum perforatum)	Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz.

Other Drugs
Based on the results of drug interaction studies, no dosage adjustment is recommended when efavirenz is given with the following: aluminium/magnesium hydroxide antacids, azithromycin, cetirizine, famotidine, fluconazole, lamivudine, lorazepam, nelfinavir, and zidovudine.
Specific drug interaction studies have not been performed with efavirenz and NRTIs other than lamivudine and zidovudine. Clinically significant interactions would not be expected since the NRTIs are metabolized via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Pregnancy
Malformations have been observed in fetuses from efavirenz-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 efavirenz. Barrier contraception should always be used in combination with the other methods of contraception (e.g. oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz.
There are no adequate and well-controlled studies in pregnant women. Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.

Lactation
Since animal data suggest that efavirenz may be passed into breast milk, it is recommended that mothers taking efavirenz do not breast-feed their infants. It has also been recommended that HIV-infected women do not breast feed their infants in order to avoid transmission of HIV.

Side effects
The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms, psychiatric symptoms and rash

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