Stovirenz®

Efavirenz

FORMS AND PRESENTATION

Stovirenz®: Film coated tablets: Jar of 30 FCT.

COMPOSITION

Stovirenz®: Each film coated tablet contains Efavirenz 600mg.

Excipients: microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, iron oxide yellow, polyethylene glycol.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Antivirals for systemic use.

ATC code: J05AG03.

Efavirenz is a NNRTI of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases (α, β, γ or δ). The free concentration of Efavirenz required for 90 to 95% inhibition of wild type or zidovudine-resistant laboratory and clinical isolates in vitro ranged from 0.46 to 6.8 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/-monocyte cultures.

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 1600 mg administered to uninfected volunteers. Dose related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3 - 5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6 - 7 days.

In HIV infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. the AUC and C_{max} of a single 600 mg dose of Efavirenz film-coated tablets in uninfected volunteers was increased by 28% (90% CI: 22-33%) and 79% (90% CI: 58-102%), respectively, when given with a high fat meal, relative to when given under fasted conditions.

Distribution

Efavirenz is highly bound (approximately 99.5 - 99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n = 9) 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 3-fold higher than the non-protein-bound (free) fraction of Efavirenz in plasma.

Biotransformation

Studies in humans and in vitro studies using human liver microsomes have demonstrated that Efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The in vitro studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for Efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. In in vitro studies Efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of Efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. In uninfected volunteers, multiple doses of 200 - 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 - 42% lower) and a shorter terminal half-life compared with single dose administration.

Elimination

Efavirenz has a relatively long terminal half-life of at least 52 hours after single doses and 40 - 55 hours after multiple doses. Approximately 14 - 34% of a radio-labeled dose of Efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged Efavirenz.

INDICATIONS

Stovirenz® is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 years of age and older.

Stovirenz® has not been adequately studied in patients with advanced HIV disease, namely in patients with CD4 counts < 50 cells/mm^3, or after failure of protease inhibitor (PI) containing regimens. Although cross-resistance of Stovirenz® with PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based combination therapy after failure of regimens containing Stovirenz®.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Efavirenz must not be used in patients with severe hepatic impairment (Child Pugh Class C).
- Efavirenz must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for CYP3A4 by Efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects (for example, cardiac arrhythmias, prolonged sedation or respiratory depression).
- Herbal preparations containing St. John's Wort *(Hypericum perforatum)* must not be used while taking Efavirenz due to the risk of decreased plasma concentrations and reduced clinical effects of Efavirenz.

PRECAUTIONS

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 (NNRT Is), 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.

Co-administration of Efavirenz with the fixed combination tablet containing Efavirenz, emtricitabine, and tenofovir disoproxil fumarate is not recommended.

Patients should be advised that current antiretroviral therapy, including Efavirenz, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

If any antiretroviral medicinal product in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medicinal products. The antiretroviral medicinal products 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 resistant virus.

- Rash: Mild-to-moderate rash has been reported in clinical studies with Efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with Efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with Efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus.

Experience with Efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Efavirenz is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking another NNRTI.

- Psychiatric symptoms: Psychiatric adverse reactions have been reported in patients treated with Efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of Efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits.
- Nervous system symptoms: Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving Efavirenz 600 mg daily in clinical studies. 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 if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.
- Seizures: Convulsions have been observed in patients receiving Efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolized by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with Efavirenz. Caution must be taken in any patient with a history of seizures.
- Hepatic events: Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.
- Effect of food: The administration of Efavirenz with food may increase Efavirenz exposure and may lead to an increase in the frequency of adverse reactions. It is recommended that Efavirenz be taken on an empty stomach, preferably at bedtime.
- Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and pneumonia caused by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.
- Lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesized. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.
- Osteonecrosis: Although the etiology 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.
- 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: 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. 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 in clinical studies to determine whether they respond differently than younger patients.
- Pediatric population: Efavirenz has not been evaluated in children below 3 years of age or who weigh less than 13 kg. Therefore, Efavirenz should not be given to children less than 3 years of age.

Rash was reported in 26 of 57 children (46%) treated with Efavirenz during a 48-week period and was severe in three patients. 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.

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

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.

Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Because of the long half-life of Efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Efavirenz is recommended.

It is unknown whether Efavirenz is excreted in human milk. Risk to the infant can not be excluded. Breastfeeding 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 inducer of CYP3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with Efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity.
- 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.
- St. John's Wort (*Hypericum perforatum*): Co-administration of Efavirenz and St. John's Wort or herbal preparations containing St. John's Wort is contraindicated. Plasma levels of Efavirenz can be reduced by concomitant use of St. John's Wort due to induction of drug metabolizing enzymes and/or transport proteins by St. John's Wort. If a patient is already taking St. John's Wort, stop St. John's Wort, check viral levels and if possible Efavirenz levels. Efavirenz levels may increase on stopping St. John's Wort and the dose of Efavirenz may need adjusting. The inducing effect of St. John's Wort may persist for at least 2 weeks after cessation of treatment.
- Protease inhibitors: Co-administration of Efavirenz with atazanavir/ritonavir is not recommended. If the co-administration of atazanavir with an NNRTI is required, an increase in the dose of both atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with Efavirenz could be considered with close clinical monitoring.
Co-administration of darunavir 300 mg twice daily, ritonavir 100 mg twice daily and Efavirenz 600 mg once daily, results in a decrease of darunavir AUC and C_{min} due to CYP3A4 induction and an increase in Efavirenz AUC and C_{min} due to CYP3A4 inhibition. Similar findings are expected with the approved darunavir/ritonavir 600/100 mg twice daily dose. This combination should be used with caution.
Co-administration of fosamprenavir, saquinavir and Efavirenz is not recommended as the exposure to both PIs is expected to be significantly decreased.
The clinical significance of decreased indinavir concentrations has not been established when co-administering indinavir and Efavirenz. Nevertheless, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both Efavirenz and indinavir.
With Efavirenz, an increase of the lopinavir/ritonavir soft capsule or oral solution doses by 33% should be considered (4 capsules/~6.5 ml twice daily instead of 3 capsules/5 ml twice daily). Caution is warranted since this dose adjustment might be insufficient in some patients. The dose of lopinavir/ritonavir tablets should be increased to 500/125 mg twice daily when co-administered with Efavirenz 600 mg once daily.
Co-administration of ritonavir 500 mg twice daily and Efavirenz 600 mg twice daily leads to an increase in Efavirenz concentrations due to the inhibition of CYP-mediated oxidative metabolism. When using Efavirenz with low-dose ritonavir, the possibility of an increase in the incidence of Efavirenz-associated adverse events should be considered.
- Antibiotics: A rash developed in 46% of uninfected volunteers receiving Efavirenz and clarithromycin. A decrease in clarithromycin concentrations and an increase in clarithromycin 14-hydroxymetabolite concentrations were noticed. The clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered.
- Antimycobacterials: Rifabutin concentrations are decreased when co-administered with Efavirenz. The daily dose of rifabutin should be increased by 50% when administered with Efavirenz. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with Efavirenz.
Co-administration of rifampicin and Efavirenz leads to a decrease in Efavirenz concentrations due to CYP3A4 and CYP2B6 induction. When taken with rifampicin, increasing Efavirenz daily dose to 800 mg may provide exposure similar to a daily dose of 600 mg when taken without rifampicin. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment.
- Antifungals: Co-administration of itraconazole and Efavirenz leads to a decrease in itraconazole concentrations by CYP3A4 induction. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Co-administration of posaconazole and Efavirenz leads to a decrease in posaconazole concentrations by UDP-G induction. Concomitant use of posaconazole and Efavirenz should be avoided unless the benefit to the patient outweighs the risk.
When Efavirenz is co-administered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg twice daily 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.
- Anticoagulants: Plasma concentrations and effects of warfarin are potentially increased or decreased by Efavirenz. Dose adjustment of warfarin may be required.
- Anticonvulsants: Co-administration of carbamazepine and Efavirenz leads to a decrease in carbamazepine concentrations by CYP3A4 induction and a decrease in Efavirenz concentrations by CYP3A4 and CYP2B6 induction. No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.
There is a potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP450 isoenzymes when co-administered with Efavirenz. When Efavirenz is co-administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic monitoring of anticonvulsant levels should be conducted.
- Selective Serotonin Reuptake Inhibitors (SSRIs): Co-administration of sertraline and Efavirenz leads to a decrease in sertraline concentrations. Sertraline dose increases should be guided by clinical response.
- Calcium channel blockers: Co-administration of diltiazem and Efavirenz leads to a decrease in diltiazem concentrations. Dose adjustments of diltiazem should be guided by clinical response.
When Efavirenz is co-administered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme (such as verapamil, felodipine, nifedipine and nicardipine), there is a potential for reduction in the plasma concentrations of the calcium channel blocker. Dose adjustments of calcium channel blockers should be guided by clinical response.
- HMG Co-A Reductase Inhibitors: Co-administration of atorvastatin, pravastatin or simvastatin with Efavirenz leads to a decrease in the concentrations of the HMG Co-A Reductase Inhibitors. Cholesterol levels should be periodically monitored. Dose adjustment of atorvastatin, pravastatin or simvastatin may be required.
- Hormonal contraceptives: Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives when co-administered with Efavirenz.
- Immunosuppressants: When co-administering immunosuppressants metabolized by CYP3A4 (e.g., cyclosporine, tacrolimus, sirolimus) and Efavirenz, decreased exposure of the immunosuppressant may be expected (CYP3A4 induction). These immunosuppressants are not anticipated to affect exposure of Efavirenz. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with Efavirenz.
-Opioids: In a study of HIV infected intravenous drug users, co-administration of Efavirenz with methadone 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.

ADVERSE EFFECTS

Frequency is defined using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); or very rare (< 1/10,000).
- Immune system disorders: Hypersensitivity (uncommon).
- Psychiatric disorders: Abnormal dreams, anxiety, depression, insomnia (common); affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis, suicide attempt, suicide ideation (uncommon); delusion, neurosis, completed suicide (rare).
- Nervous system disorders: Cerebellar coordination and balance disturbances, disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%) (common); agitation, amnesia, ataxia, abnormal coordination, convulsions, abnormal thinking, tremor (uncommon).
- Eye disorders: Blurred vision (uncommon).
- Ear and labyrinth disorders: Tinnitus, vertigo (uncommon).
- Vascular disorders: Flushing (uncommon).
- Gastrointestinal disorders: Abdominal pain, diarrhea, nausea, vomiting (common); pancreatitis (uncommon).
- Hepatobiliary disorders: Acute hepatitis (uncommon); hepatic failure (rare).
- Skin and subcutaneous tissue disorders: Rash (11.6%) (very common); pruritis (common); erythema multiforme, Stevens-Johnson syndrome (uncommon); photo-allergic dermatitis (rare).
- Reproductive system and breast disorders: Gynecomastia (uncommon).
- General disorders and administration site conditions: Fatigue (common).
- Rash: 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.
- Psychiatric symptoms: Serious psychiatric adverse reactions have been reported in patients treated with Efavirenz. Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions with frequencies ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation.
- Nervous system symptoms: Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. Nervous system symptoms may occur more frequently when Efavirenz is taken concomitantly with meals possibly due to increased Efavirenz plasma levels. Dosing at bedtime seems to improve the tolerability of these symptoms and can be recommended during the first weeks of therapy and in patients who continue to experience these symptoms. Dose reduction or splitting the daily dose has not been shown to provide benefit.
- Hepatic failure: A few of the reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.
- Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.
- Lipodystrophy and metabolic abnormalities: Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).
Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia.
- Osteonecrosis: Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.
- Pediatric population: Undesirable effects in children were generally similar to those of adult patients.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the management of HIV infection. Stovirenz® must be given in combination with other antiretroviral medicines.
It is recommended that Stovirenz® be taken on an empty stomach. The increased Stovirenz® concentrations observed following administration of Stovirenz® with food may lead to an increase in frequency of adverse reactions.
In order to improve the tolerability of nervous system undesirable effects, bedtime dosing is recommended.
- Adults and adolescents over 40 kg: The recommended dose of Stovirenz® in combination with nucleoside analogue reverse transcriptase inhibitors (NRTIs) with or without a PI is 600 mg orally, once daily.
Stovirenz® film-coated tablets are not suitable for children weighing less than 40 kg.
- Dose adjustment: If Stovirenz® is co-administered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the Stovirenz® dose must be reduced by 50%, i.e., to 300 mg once daily. When treatment with voriconazole is stopped, the initial dose of Stovirenz® should be restored.
If Stovirenz® is co-administered with rifampicin, an increase in the dose of Stovirenz® to 800 mg/day may be considered.

Renal impairment

The pharmacokinetics of Stovirenz® have not been studied in patients with renal insufficiency; however, less than 1% of the Stovirenz® dose is excreted unchanged in the urine, so the impact of renal impairment on Stovirenz® elimination should be minimal.

Hepatic impairment

Patients with mild liver disease may be treated with their normally recommended dose of Stovirenz®. Patients should be monitored carefully for dose-related adverse reactions; especially nervous system symptoms.

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 remove significant quantities of it from blood.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.
Date of revision: June 2015.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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