Avifanz®

Tablet

Description

Avifanz is the brand name for Efavirenz. Efavirenz, a synthetic anti-retroviral agent, is a non-nucleoside reverse transcriptase inhibitor. While Efavirenz is pharmacologically related to other non-nucleoside reverse transcriptase inhibitors, Efavirenz differs structurally from these drugs and also differs structurally from other currently available anti-retroviral agents.

Indications

Avifanz (Efavirenz) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV- RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long term suppression of HIV-RNA with Avifanz.

Dosage and Administration

Adults : The recommended dosage of Avifanz is 600 mg orally, once daily, in combination with a protease inhibitor and or nucleoside analogue reverse transcriptase inhibitors (NRTIs). Avifanz may be taken with or without food; however, a high fat meal may increase the absorption of Avifanz 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.

Concomitant antiretroviral therapy : Avifanz must be given in combination with other antiretroviral medications.

Paediatric patients : The following table describes the recommended dose of Avifanz for paediatric patients 3 years of age or older and weighing between 10 and 40 Kg.

Table 1 : Paediatric Dose to be Administered Once Daily		
Body Weight		**Avifanz**
Kg	Lbs	Dose (mg)
10 to < 15	22 to < 33	200
15 to < 20	33 to < 44	250
20 to < 25	44 to < 55	300
25 to < 32.5	55 to < 71.5	350
32.5 to < 40	71.5 to < 88	400
40 ≤	88 ≤	600

Contraindications

Efavirenz is contraindicated in patients with known hypersensitivity to the drug or any ingredient in formulation.

Precautions

Warning : High fat foods may cause unwanted increases in drug effect. Avoid taking the drug with high-fat foods or take on an empty stomach. Regular, periodic measurement of plasma HIV-1 RNA levels and CD4+ T-cell counts is necessary to determine the risk of disease progression and to determine when to modify anti-retroviral agent regimens. Patients should be advised that Efavirenz has not been shown to reduce the risk of transmission of HIV to others via sexual contact or blood contamination, and that practices designed to prevent transmission of HIV should be maintained during anti-retroviral therapy. Efavirenz should always be administered in conjunction with other anti-retroviral agent and should not be used alone in the treatment of HIV infection. Although Efavirenz used in combination with other anti-retroviral agents appears to be well tolerated, patients should be monitored closely for adverse effects during combination therapy. The usual precautions and contraindications of the other anti-retrovirals in the regimen should be considered during combination therapy; Efavirenz should not be added as sole agent to a failing regimen. Whenever a change in anti-retroviral therapy is considered because of therapeutic failure, at least 2 components of the previous regimen should be changed since adding a single new agent may predispose to the development of viral resistance. Use of an entirely new regimen containing at least 3 drugs is preferred. The effect of Efavirenz therapy on subsequent therapy with other non-nucleoside reverse transcriptase inhibitors remains to be determined.

Because cross-resistance occurs among non-nucleoside reverse transcriptase inhibitors, most clinicians suggest that individuals who experience disease progression while receiving one of the agents (e.g., Delavirdine, Efavirenz, Nevirapine) should not be switched to another agent in the class. As Efavirenz has been associated with adverse CNS effect, patients' should be advised that the drug may impair their ability to perform hazardous activities requiring mental alertness or physical coordination such as operating machinery or driving a motor vehicle. In addition, patients' receiving Efavirenz should be informed that there is a potential for additive CNS effects if they use Efavirenz concomitantly with psychoactive drugs or alcohol. Patients' should be advised to contact their clinician if they experience delusions, inappropriate behaviour, or acute depression while receiving Efavirenz; discontinuance of the drug may be necessary in patients' who experience such CNS effects. Efavirenz is metabolised in the liver; it should be used with caution in patents with hepatic impairment. Serum hepatic enzyme concentrations should be monitored during Efavirenz therapy in patients who have, or may have, Hepatitis B and/or C virus infection, in patients receiving concomitant ritonavir and in patients receiving concomitant therapy with hepatotoxic drugs. In patients with serum hepatic enzyme concentrations more than 5 times the upper limit of normal, the benefits of continued Efavirenz therapy versus the risks of hepatotoxicity should be considered. Because increases in serum cholesterol concentration have occurred in individuals receiving Efavirenz, cholesterol monitoring should be considered in patients receiving the drug. Because of the risk of foetal malformations, Efavirenz should not be used in women who are or may become pregnant unless no other therapeutic options exist.

Paediatric precautions : Safety and efficacy of Efavirenz in neonates and children younger than 3 years of age or who weigh less than 13 kg have not been evaluated. Adverse effects reported in children receiving Efavirenz are similar to those reported in adults including CNS, GI and dermatologic effects. Adverse CNS effects occurred in 9% of children receiving Efavirenz. In clinical studies rash has been reported more frequently in children than adults (40 *vs* 27.3%) and the incidence of moderate to severe rash has been greater in children than adults. Because of the high incidence of dermatologic reactions in children, antihistamines may be used for the prevention of rash when initiating

Efavirenz therapy in children; however, the efficacy of such a strategy has not been determined.

Drug Interactions

Drugs which induce activity (eg, Phenobarbital, Rifampin, Rifabutin) would be expected to increase the clearance of Efavirenz resulting in lowered plasma concentrations. Drug interactions with Efavirenz are summarised in Table 2.

Table-2 : Drugs that Should Not be Co-administered with Efavirenz

Drug class		**Drugs within class not to be coadministered with Efavirenz**
Antihistamines, Benzodiazepines, GI Motility agents, Anti-Migraine, Antifungal		Astemizole, Midazolam, Triazolam, Cisapride, ergot derivatives
Established Drug Interactions		
Drug Name	**Effect**	**Clinical Comment**
Atazanavir	↓Atazanavir concentration	When coadministered with Efavirenz in treatment-naive patients, the recommended dose of Atazanavir is 300 mg with Ritonavir 100 mg and Efavirenz 600 mg (all once daily). Dosing recommendations for Efavirenz and Atazanavir in treatment-experienced patients have not been established.
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 Azithromycin, should be considered. Other macrolide antibiotics, such as Erythromycin, have not been studied in combination with Efavirenz.
Indinavir	↓Indinavir concentration	The optimal dose of Indinavir, when given in combination with Efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased Indinavir metabolism due to Efavirenz. When Indinavir at an increased dose (1000 mg every 8 hours) was given with Efavirenz (600 mg once daily), the Indinavir AUC and Cmin were decreased on average by 33-46% and 39-57%, respectively, compared to when Indinavir (800 mg every 8 hours) was given alone.

Table-2 : Drugs that Should Not be Co-administered with Efavirenz		
Drug Name	**Effect**	**Clinical Comment**
Lopinavir/Ritonavir	↓lopinavir concentration	A dose increase of Lopinavir/Ritonavir to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food is recommended when used in combination with Efavirenz.
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 oestradiol	↑Ethinyl oestradiol concentration	Plasma concentrations increased by Efavirenz clinical significance unknown. Because the potential interaction of Efavirenz with oral contraceptives has not been fully characterised, 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 (eg, dizziness, nausea, paraesthesia) 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.
Sertraline	↓Sertraline concentration	Increases in Sertraline dose should be guided by clinical response

Table 2: Drugs That Should Not be Co-administered with Efavirenz	
Other Potentially Clinically Significant Drug or Herbal Product Interactions With Efavirenz	
Anticoagulant: Warfarin	Plasma concentration 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 level 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 inhibitor : Saquinavir/Ritonavir combination	No pharmacokinetic data are available.
Amprenavir	Efavirenz has the potential to decrease serum concentrations of Amprenavir.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	No studies have been performed with other NNRTIs.
St. John's wort *(Hypericum perforatum)*	Expected to substantially decrease plasma level of Efavirenz has not been studied in combination with Efavirenz.

Other drugs : Based on the results of drug interaction studies in Tables 2, no dosage adjustment is recommended when Efavirenz is given with the following : Aluminum/Magnesium hydroxide antacids, Azithromycin, Cetirizine, Famotidine, Fluconazole, Lamivudine, Lorazepam, Nelfinavir, Paroxetine, 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 metabolised via a different route than Efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.

Side Effects

CNS effects : Dizziness, impaired concentration, abnormal dreams and insomnia have been reported in about 52% of adults receiving Efavirenz 600 mg once daily. In clinical studies these adverse effects were reported

in 26% of adults in the control groups not receiving Efavirenz. These CNS effects were described as mild (do not interfere with daily activities) in 31.4%, moderate (may interfere with daily activities) in 17.8% or severe (interrupt usual daily activities) in 2.6% cases. These effects generally begin during the first 1-2 days of therapy, improve with continued therapy and usually resolve after the first 1-2 days of Efavirenz therapy. Adverse CNS effects may be more tolerable if the daily dose of Efavirenz is administered at bedtime, especially during the first 2-4 weeks of therapy and in patients who continue to experience such effects. Fatigue has been reported in up to 7% of adults receiving Efavirenz in clinical studies.

Severe acute depression, sometimes accompanied by suicidal ideation / attempts, has been reported rarely in patients receiving Efavirenz in clinical studies.

Adverse CNS effects occurred in 9% of children receiving Efavirenz in clinical studies.

Dermatologic and sensitivity reactions : Rash has occurred in 27.3% of adults receiving Efavirenz in clinical studies and in 17% of adults in control groups not receiving the drug. Pruritus or increased sweating has been reported in 1-2% of patients. Allergic reaction, alopecia, eczema, folliculities, skin exfoliation or urticaria has occurred in less than 2% of patients receiving the drug.

GI effects : Nausea or diarrhoea has been reported in up to 12% of adults receiving Efavirenz. Vomiting, dyspepsia, abdominal pain, or flatulence has occurred in some Efavirenz-treated adults. Dry mouth or taste change has been reported in up to 2% of patients.

Hepatic effects : Hepatitis occurred in less than 2% of patients.

Cardiovascular effects : While the clinical importance remains to be determined, total serum cholesterol concentrations have been increased 10-20% in healthy individuals receiving Efavirenz. Hot flushes, flushing, palpitations, tachycardia, or thrombophlebitis has been reported in less than 2%, of patients.

Use in Special Populations

Pregnancy : The drug should not be used in patients who are pregnant or have potential to become pregnant.

Women taking hormone-based birth control : Women should not rely only on hormone-based birth control, such as pills, injections, or implants, because Efavirenz may make these contraceptives ineffective.

Lactation : Efavirenz may pass through breast milk and cause serious harm to the baby. It should not be used during lactation.

Commercial Pack

Avifanz® Tablet : Each box contains 1 x 10's tablets in blister strip. Each tablet contains Efavirenz INN 600 mg.