Avifix®

Tablet

Description

Avifix is a preparation of Nelfinavir (as mesylate), which is a human immunodeficiency virus (HIV) protease inhibitor available as film coated tablet (as Nelfinavir free base).

Indications

Avifix is indicated for the treatment of HIV infection when antiretroviral therapy is warranted.

Dosage and Administration

Adults : The recommended dose is 1250 mg (five 250 mg tablets) twice daily or 750 mg (three 250 mg tablets) three times daily. Avifix should be taken with a meal. Antiviral activity is enhanced when Avifix is administered in combination with nucleoside analogues. Therefore, it is recommended that Avifix should be used in combination with nucleoside analogues.

Paediatric patients (2-13 years) : The recommended oral dose of Avifix for paediatric patients 2 to 13 years of age is 20-30 mg/kg per dose, three times daily with a meal. The recommended paediatric dose of Avifix to be administered three times daily is described in following table 1 :

Table 1 : Paediatric Dose to be Administered Three Times Daily

Body Weight		Number of Level 1 gm Scoops	Number of Level Teaspoons	Number of Tablets
Kg.	Lbs.			
7 to < 8.5	15.5 to < 18.5	4	1	-
8.5 to < 10.5	18.5 to < 23	5	$1\ ^1/_4$	-
10.5 to < 12	23 to < 26.5	6	$1\ ^1/_2$	-
12 to < 14	26.5 to < 31	7	$1\ ^3/_4$	-
14 to < 16	31 to < 35	8	2	-
16 to < 18	35 to < 39.5	9	$2\ ^1/_4$	-
18 to < 23	39.5 to < 50.5	10	$2\ ^1/_2$	2
≥ 23	≥ 50.5	15	$3\ ^3/_4$	3

Contraindications
Avifix is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Co-administration of Avifix is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening adverse events.

Precautions
Warning : Avifix should not be administered concurrently with Terfenadine, Astemizole, Cisapride, Triazolam, Midazolam, Ergot derivatives, Amiodarone or Quinidine because Avifix may affect the hepatic metabolism of these drugs and create potential for serious and/or life-threatening adverse events.

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycaemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for treatment of these events. In some cases diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycaemia persisted in some cases.

Precautions : General - Nelfinavir is principally metabolised by the liver. Therefore, caution should be exercised when administering this drug to patients with hepatic impairment.

Haemophilia : There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis, in patients with haemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

Drug Interactions
Nelfinavir is an inhibitor of CYP3A (cytochrome P450 3A). Co-administration of Avifix and drugs primarily metabolised by CYP3A (e.g.,

Table 2 : Drugs that Should Not be Co-administered with Avifix	
Drug Class	**Drugs**
Antiarrhythmics	Amiodarone, Quinidine
Antihistamines	Astemizole, Terfenadine
Antimigraine	Ergot derivatives
Antimycobacterial agents	Rifampin
Benzodiazepines	Midazolam, Triazolam
GI motility agents	Cisapride

Drugs which Require a Dose Reduction when Co-administered with Avifix	
Drug Class	**Drugs**
Antimycobacterial agents	Rifabutin

Other Potential Clinically Significant Drug Interactions with Avifix *	
Anticonvulsant: Carbamazepine	May decrease Nelfinavir plasma concentration**
Anti-HIV protease inhibitors: Indinavir	May increase Nelfinavir plasma concentration
Oral contraceptives: Ethinyl oestradiol	Plasma concentration may be decreased by Avifix

* This table is not all inclusive

** Avifix may not be effective due to decreased Nelfinavir plasma concentration in patients taking these agents concomitantly.

dihydropyridine calcium channel blockers) may result in increased plasma concentration of the other drug that could increase or prolong both its therapeutic and adverse effects. Co-administration of drugs that inhibit CYP3A may increase Nelfinavir plasma concentration.

Based on known metabolic profiles, clinically significant drug interactions are not expected between Avifix and Dapsone, Trimethoprim/Sulphamethoxazole, Clarithromycin, Erythromycin, Itraconazole or Fluconazole.

Anti-HIV Protease Inhibitors

Indinavir : Co-administration of Indinavir with Avifix resulted in 83% increase in Nelfinavir plasma AUC and 51% increase in indinavir plasma AUC Currently, there are no safety and efficacy data available from the use of this combination.

Ritonavir : Co-administration of Ritonavir with Avifix resulted in a 152% increase in Nelfinavir plasma AUC and very little change in Ritonavir plasma AUC. Currently, there are no safety and efficacy data available from the use of this combination.

Saquinavir : Co-administration of Saquinavir (using an experimental soft gelatin capsule formulation of Saquinavir 1200mg) with Avifix resulted in an 18% increase in Nelfinavir plasma AUC and a 4 fold increase in Saquinavir plasma AUC. If used in combination with Saquinavir hard gelatin capsules at the recommended dose of 600 mg tid, no dose adjustments are needed. Currently, there are no safety and efficacy data available from the use of this combination.

Anti-HIV Reverse Transcriptase Inhibitors

Didanosine : It is recommended that Didanosine be administered on an empty stomach; therefore, Nelfinavir should be administered (with food) one hour after or more than two hours before didanosine.

Zidovudine : Co-administration of Zidovudine and Lamivudine with Avifix resulted in a 35% decrease in Zidovudine plasma AUC. Dose adjustment is not needed when Zidovudine is administered with Avifix. Little or no change in the pharmacokinetics of either drug was observed when Avifix was co-administered with Lamivudine or Stavudine.

Side Effects

The safety of Nelfinavir was studied in over 1500 patients who received drug either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving Nelfinavir was diarrhoea, which was generally of mild to moderate intensity.

Adverse events occurring in less than 2% of patients receiving Nelfinavir in all phase II/III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.

General : Abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain and redistribution/accumulation of body fat.

Digestive system : Anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis and vomiting.

Haemic/Lymphatic system : Anaemia, leukopenia and thrombocytopenia.

Metabolic/Nutritional : Increase in alkaline phosphate, amylase, creatinine phosphokinase, lactic dehydrogenase, SGOT, SGPT and γ glutamyl transpeptidase, hyperlipaemia, hyperuricaemia, hyperglycaemia, hypoglycaemia, dehydration and liver function tests abnormal.

Musculoskeletal system : Arthralgia, arthritis, cramps, myalgia, myasthenia and myopathy.

Nervous system : Anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paraesthesia, seizures, sleep disorder, somnolence and suicide ideation.

Respiratory system : Dyspnoea, pharyngitis, rhinitis and sinusitis.

Skin/Appendages : Dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruitus, sweating, and urticaria.

Ophthalmic : Acute iritis and eye disorder.

Urogenital system : Kidney calculas, sexual dysfunction.

Use in Special Populations

Pregnancy Category B : There are no adequate and well controlled studies in pregnant women.

Lactation : The US Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid postnatal transmission of HIV to a child.

Paediatric use : The safety, effectiveness and pharmacokinetics of Nelfinavir have not been evaluated in paediatric patients below the age of 2 years.

Commercial Pack

Avifix® Tablet : Each box contains 1 x 10's tablets in blister strip. Each tablet contains Nelfinavir (as mesylate) INN 250 mg.