PRESENTATION:
Adiva® Tablet: Each film coated tablet contains Efavirenz INN 600 mg.

PHARMACOLOGY:
Adiva® (Efavirenz) is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Efavirenz (EFV) activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT).
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 Cmax 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 were approximately 3-5 hours and steady-state plasma concentrations were reached in 6-10 days.
Effect of food on oral absorption: Administration of a single 600-mg Efavirenz tablet with a high-fat/high-caloric meal (approximately 1000 kcal, 500-600 kcal from fat) was associated with a 28% increase in mean AUC of Efavirenz and a 79% increase in mean Cmax of Efavirenz relative to the exposures achieved under fasted conditions
Distribution: Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin.
Metabolism: Efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. The in vitro studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for Efavirenz metabolism.
Elimination: Efavirenz has a terminal half-life of 52-76 hours after single doses and 40-55 hours after multiple doses. Nearly all of the urinary excretion of the drug was in the form of metabolites.

INDICATION AND USES:
Adiva® in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection.

DOSAGE AND ADMINISTRATION:
It is recommended that Adiva® be taken on an empty stomach, preferably at bedtime.
Adults: The recommended dosage of Adiva® is 600 mg orally, once daily, in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs).
Pediatric Patients: Following table describes the recommended dose of Adiva® for pediatric patients 3 years of age or older and weighing between 10 and 40 kg. The recommended dosage of Adiva® for pediatric patients weighing greater than 40 kg is 600 mg, once daily.

Body weight (Kg)	Adiva® : Dose (mg)
10 to <15	200
15 to < 20	250
20 to < 25	300
25 to < 32.5	350

32.5 to < 40 400
40 600

CONTRAINDICATION:
Efavirenz is contraindicated in patients with clinically significant hypersensitivity to any of its components.

WARNING:
Efavirenz must not be used as a single agent to treat HIV-1 infection 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.

ADVERSE ACTION AND PRECAUTION:
The most significant adverse events observed in patients treated with Efavirenz are nervous system symptoms, psychiatric symptoms, and rash.
Nervous System Symptoms: These symptoms include dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations. 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 nervous system symptoms.

Psychiatric Symptoms: Severe psychiatric adverse experiences have been reported in patients treated with efavirenz. They are: severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behavior, paranoid reactions, and manic reactions.
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. Pancreatitis has been reported, 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.
Other rarely occurred adverse effects are:
Body as a Whole- allergic reactions, asthenia, redistribution/accumulation of body fat
Central and Peripheral Nervous System- abnormal coordination, ataxia, convulsions, hypoesthesia, paresthesia, neuropathy, 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
Respiratory- dyspnea
Skin and Appendages- erythema multiforme, nail disorders, photoallergic dermatitis, skin discoloration, Stevens-Johnson syndrome

Special Senses- abnormal vision, tinnitus

DRUG INTERACTION:
Efavirenz should not be administered concurrently with astemizole, cisapride, midazolam, triazolam, or ergot derivatives because competition for CYP3A4 by Efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). Efavirenz should not be administered concurrently with voriconazole because Efavirenz significantly decreases voriconazole plasma concentrations.
The following medicines may need to be replaced with another medicine when taken with Efavirenz: saquinavir, clarithromycin. The following medicines may need to have their dose changed when taken with Efavirenz: indinavir, lopinavir/ritonavir, rifabutin, atazanavir sulfate (If Efavirenz and atazanavir are taken, ritonavir should also be taken), sertraline.

USE IN PREGNANCY AND LACTATION:
Pregnancy category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving Efavirenz. Women of childbearing potential should undergo pregnancy testing before initiation of Efavirenz.

The Centers for Disease Control and Prevention recommend that HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Although it is not known if Efavirenz is secreted in human milk, Efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, mothers should be instructed not to breast-feed if they are receiving Efavirenz.

PAEDIATRIC USE:
Efavirenz has not been studied in pediatric patients below 3 years of age or who weigh less than 10 kg.

STORAGE CONDITION:
Store at a cool and dry place. Protect from light and moisture.
Keep the medicine out of the reach of children.

HOW SUPPLIED:
Adiva® Tablet: Each box contains 1 x 10 tablets in blister pack.