

Efavirenz (Sustiva®)

Class:

Efavirenz is a benzoxamine compound.

Antiviral Activity:

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are highly selective for HIV-1 but do not exhibit activity against other viruses.

Mechanism of Action:

NNRTIs bind noncompetitively to an active site of the reverse transcriptase molecule. Reverse transcriptase directs the polymerization of DNA from viral RNA. The NNRTIs inhibit this polymerization by altering the position of critical amino acids within the catalytic site.

Mechanism of Resistance:

Resistance of NNRTIs occurs through mutations of the reverse transcriptase gene in the viral genome. When nonnucleoside reverse transcriptase inhibitors are used as monotherapy for HIV-1 infection, drug resistance develops rapidly. NNRTI naïve patients with prior nucleoside analogue reverse transcriptase inhibitor (NRTI) exposure, who have isolates with resistance mutations and phenotypic resistance to NRTIs, appear more likely to have hypersusceptibility to the NNRTI class of drugs.

Pharmacodynamics:

The *in vitro* 90% inhibitory concentration of efavirenz for HIV-1 ranges from 1.7 to 25 nM. After adjustment for protein binding, these inhibitory concentrations range between 0.34 to 5 µM.

Pharmacokinetics:

Efavirenz is well absorbed after oral administration and peak efavirenz concentrations are attained by 5 hours after dosing. Steady-state plasma concentrations are reached in 6-10 days. Increases in AUC and C_{max} are seen with the administration of efavirenz with a high-fat meal (>54 g fat) and should be avoided. Efavirenz is approximately 99% plasma protein bound.

At standard adult doses, efavirenz exhibits linear pharmacokinetics. Efavirenz is principally metabolized by CYP450 2B6 and 3A4 to hydroxylated metabolites with subsequent glucuronidation. Efavirenz is an inducer and an inhibitor of the cytochrome P450 system and leads to self-induction.

Adverse Effects:

The most common adverse effects with efavirenz therapy are central nervous system symptoms, rash and hepatitis.

Dosage:

Capsule – 50mg (90 capsule bottle), 100mg (90 capsule bottle), 200mg (90 capsule bottle)
Tablet – 600mg (30 tablet bottle)

Adult dosing:
600 mg daily

Pediatric Dosing:

10 kg to < 15 kg – 200mg daily
15 kg to < 20 kg – 250mg daily
20 kg to < 25 kg – 300mg daily
25 kg to < 32.5 kg – 350mg daily
32.5 kg to < 40 kg – 400mg daily
> 40 kg – 600mg daily

Take on an empty stomach preferably at night

Disease state based dosing:

Dose adjustments in renal dysfunction do not appear to be necessary.

Use with caution in patients with impaired hepatic function.

Contraindications/Warnings/Precautions:

Do not give in combination with agents that are highly dependent on metabolism through CYP450 3A4.

Do not give during pregnancy due to the risk of fetal malformations.

Drug Interactions:

Efavirenz is principally metabolized by CYP450 2B6 and 3A4 to hydroxylated metabolites with subsequent glucuronidation. *In vitro*, efavirenz is an inhibitor of CYP3A4, CYP2C9, and CYP2C19. However, its effect on CYP3A4 is mixed, as it has also been shown to induce this enzyme. Therefore, medications that are metabolized through CYP2B6, 3A4, 2C9 and 2C19 as well as those that glucuronidated may interact with efavirenz.

Pregnancy:

Category D: Risk established, but benefits may outweigh risk.

Efavirenz has demonstrated rodent teratogenicity and caused malformations in 3 of 20 fetal cynomolgous monkeys. These malformations included anencephaly, anophthalmia and microphthalmia. Therefore, efavirenz should not be administered during pregnancy.

Monitoring Requirements:

NNRTIs are suitable for TDM for several reasons, including considerable interpatient variability in concentrations among patients who take the same dose and data indicating relationships between the concentration of drug in the body, the anti-HIV effect and in some cases, toxicity.

Liver function tests, cholesterol and triglycerides should be monitored in patients taking efavirenz.

Brand names/Manufacturer:

Sustiva®

50mg capsule, 100mg capsule, 200mg capsule and 600mg tablet – Bristol-Myers Squibb.