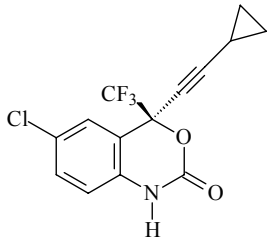
Efavirenz (Sustiva®)

Submitted by Dr. Peter Singer, Alberta Justice Medical Examiner, Edmonton, Canada **January 30, 2002**

Manufacturer: DuPont Pharmaceuticals
Chemical Name: (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one
FDA Approval: September 17, 1998
Use: Antiviral, (reverse transcriptase inhibitor) used with other anti-HIV medication
Molecular Formula: $C_{14}H_9ClF_3NO_2$
Molecular Weight: 315.68



Half-Life T1/2: 52-76 h single dose, 40-55 h after 10 days of continuous use.
PKa: 10.2
Dose: Capsules of 50, 100 and 200 mg. Initial dose 600 mg once /day.
Binding: >99% protein bound.
Absorption: Peaks 3-5 hours after dose and steady-state is reached after 6-10 days. After 600 mg/day doses steady state levels are C_{max} 4.1 ± 1.1 mg/l (12.9 ± 3.7 μM) C_{min} 1.7 ± 1.0 mg/l (5.6 ± 3.2 μM) and AUC 58 ± 23 mg.h (184 ±73 uM.h). Levels are dose proportional. Peak plasma concentrations are 0.5 to 2.9 mg/l (1.6 to 9.1 μM) after single doses of 100 to 1600 mg.
Drug interactions: Inhibits CYP2C9, CYP2C19 and inhibits (in vitro)/induces (in vivo) CYP3A4. Avoid astemizole, midazolam, triazolam, cisapride, ergot and St John's wort.
Metabolism: Metabolised by CYP3A4 and CYP2B6 to hydroxy metabolites with subsequent glucuronidation. Induces its own metabolism.
Adverse effects: Dizzyness, impaired concentration, somnolence, depersonalization, abnormal dreams, insomnia and rash. May be habit forming. There is a low incidence of very severe psychiatric symptoms including severe depression or mania, suicidal ideation, hallucinations and possible psychosis. Adverse effects may begin within a day or two of initiating therapy and often resolve within 2 to 4 weeks.
Patients should be alerted to the potential for additive central nervous system effects in combination with ethanol.
Extraction: **Information** Liquid-liquid chlorobutane extraction at ph 8 extracts well, (see fig. 1), however, it does not survive an acid back-extraction / clean-up step (see fig. 2). Is Insoluble in water.
Instrumentation: Readily detected by NPD, ECD and GC/MSD (see MS, fig. 3). Oven program 80° hold for 0.5 min to 300° at 20° / minute, hold for 3 min. HP5 column, 10 m x 0.25 mm id x 0.5 μm film thickness. Elutes at 8.07 min, (internal standards elute at: mepivacaine 7.69 min, SKF525 at 8.80 min and prazepam at 10.06 min). Not quantitated.
Occurrence: Readily detected in blood. Also small amounts are found in urine, co-occurring with large amounts of the hydroxy compound (see MS, fig. 4); the hydroxy metabolite(s) elute(s) in a broad peak, 0.27 minutes after the parent.
May give false positive urine cannabinoid immunoassay (CEDIA DAU) test.

Fig 1: Efavirenz TIC (pH8 extraction)

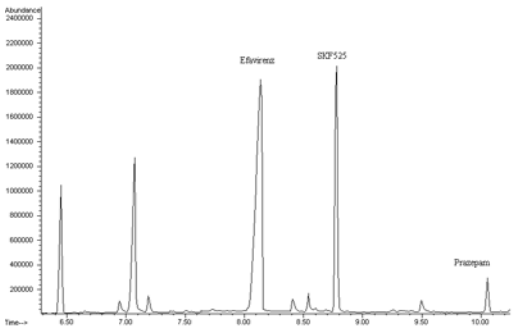


Fig2: Efavirenz TIC (acid back-extraction)

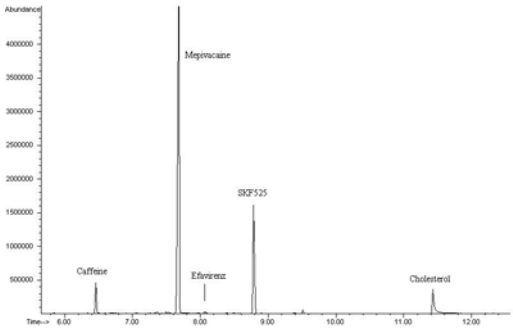


Fig 3: MS fragmentation Efavirenz (246, 180, 315)

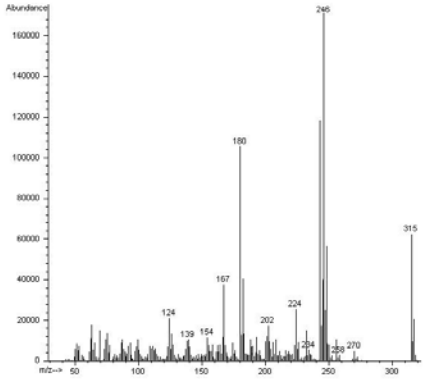


Fig 4: MS Fragmentation Hydroxy-Efavirenz (282, 196, 331)