Selected Properties of Efavirenz

Other names	Sustiva® (North America), Stocrin® (Europe), DMP-266 Combination formulations: • Atripla®: efavirenz/emtricitabine/tenofovir
Manufacturer	Bristol-Myers Squibb Canada
Pharmacology/Mechanism of Action	Non-competitive, selective binding to reverse transcriptase enzyme causing conformational change that inactivates the catalytic site, preventing proviral DNA synthesis in HIV-1. Does not require intracellular phosphorylation.
Activity	$IC_{90\text{-}95}$: 1.7 - ≤25 nM (wild-type)
Resistance - genotypic	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations) *L100I*#, **K103N***, ***V106M****, V108I, *Y181C/I*#, **Y188L***, *G190S/A*#, P225H ***multi-NNRTI resistance** #*accumulation of ≥2 leads to multi-NNRTI resistance*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/) K103N: 19-fold ↑ (high resistance) V106A: 1.9-fold ↑ (low resistance) Y188L: 130-fold ↑ (high resistance) G190A: 7-fold ↑ (intermediate resistance) G190S: 52-fold ↑ (high resistance) Multiple mutations confer high-level resistance (100-200 fold) to efavirenz: L100I + K103N: 274-fold ↑ (high resistance) G190A + K103N: 213-fold ↑ (high resistance) K103N + P225H: 100-fold ↑ (high resistance) K103N +Y188L: 270-fold ↑ (high resistance)
Cross-Resistance	K103N mutation confers high-level resistance to other NNRTIs. In vitro, efavirenz retains activity against variants containing V106A, Y181C, Y188C, G190A, and P236L mutations (all reported with other NNRTI therapies). Cross-resistance between efavirenz and protease inhibitors or nucleoside analogues unlikely because enzyme targets are different.
Oral Bioavailability	
Effect of Food	Can take with or without food. High fat meal (670 kcal, 60% fat, 400 kcal fat) may ↑ EFV concentrations by 50%.
Protein Binding	99.75% (albumin)

Vd	
Tmax	3 - 5 hours
serum T ½	40-55 hours after multiple doses
Drug Concentrations	Dose-related increases in Cmax and AUC seen for doses up to 1600 mg; may have diminished absorption at higher doses. In 35 patients receiving efavirenz 600 mg once daily, steady-state Cmax was 12.9 ± 3.7 µM (mean ± SD), steady state Cmin was 5.6 ± 3.2 µM, and AUC was 184 ± 73 µM•h.
Minimum target trough concentrations (for wildtype virus)	Cmin: >1000 ng/mL Cmax: <4000 ng/mL
CSF (% of serum)	In HIV-1 infected patients (n=9) who received efavirenz 200-600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma. 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010] Paired CSF and plasma samples were obtained from patients taking standard doses of efavirenz. Efavirenz concentrations were 0.5% of plasma concentrations. Efavirenz CSF concentrations:IC50wt (0.51 ng/mL) ratio was 26 (IQR 8-41). Two CSF concentrations (2.6%) were below the IC50.[Best B et al. CROI 2009] In a patient with cryptococcal meningitis, plasma and CSF efavirenz concentrations were measured over 24 hours. The median plasma efavirenz concentration was 3,718 ng/ml (range, 2,439 to 4,952), and the median CSF concentration was 16.3 ng/ml (range, 7.3 to 22.3). The CSF/plasma area-under-the-curve ratio was 0.0044 corresponding to a CSF penetration of 0.44% of plasma.[Yilmaz et al. 2012]
Metabolism	Metabolism primarily via CYP 3A4, and 2B6; undergoes autoinduction (20-40%) during first two weeks of therapy; major metabolite (inactive): glucuronide conjugate
Excretion	14-34% (primarily hydroxylated metabolites) excreted in urine, 16-61% in feces.
Dosing – Adult	600 mg once daily preferably before bedtime. Can take with food, however high fat foods may increase the absorption by 50%, thus potentially increasing side effects. **NB: Efavirenz is contraindicated in pregnancy; women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.**

Dosing – Pediatric

Infants/children (at least 3 months of age and weighing between 3.5-40 kg):

Patient Body Weight	SUSTIVA Daily Dose	Number of Capsules[a] or Tablets[b] and Strength to Administer
3.5 kg to less than 5 kg	100 mg	two 50 mg capsules
5 kg to less than 7.5 kg	150 mg	three 50 mg capsules
7.5 kg to less than 15 kg	200 mg	one 200 mg capsule
15 kg to less than 20 kg	250 mg	one 200 mg + one 50 mg capsule
20 kg to less than 25 kg	300 mg	one 200 mg + two 50 mg capsules
25 kg to less than 32.5 kg	350 mg	one 200 mg + three 50 mg capsules
32.5 kg to less than 40 kg	400 mg	two 200 mg capsules
at least 40 kg	600 mg	one 600 mg tablet OR three 200 mg capsules

[a]Capsules can be administered intact or as sprinkles

[b]Tablets must not be crushed

Special instructions for pediatric patients

Give at bedtime during first 2-4 weeks of therapy to decrease CNS effects

Flavoured pediatric suspension available via expanded access (1-877-372-7097).

Can open **capsules** and mix powder with two teaspoons of one of four possible food vehicles: applesauce, grape jelly, yogurt, or infant formula (but may result in hot "jalapeno" sensation) [Kaul et al. AJHP 2010;67:217-22].

1. Hold the capsule vertically with the cap facing up.

2. Pull the cap away from the body of the capsule carefully, sprinkle and mix the contents with the food in a 100-mL container.

3. Administer the mixture with a spoon as soon as possible but no more than 30 minutes after mixing.

4. After administration of the efavirenz–food mixture, an additional small amount (approximately 2 teaspoons) of food or formula must be added to the empty mixing container, stirred to disperse any remaining efavirenz residue, and administered to the patient.

For nasogastric administration, may open capsules and mix with either 5 mL MCT oil or 15 mL Ora-Sweet (grind powder first to enhance dissolution). Powder is insoluble in water; do NOT mix with polyethylene glycol (will ↓ bioavailability).

Efavirenz tablets may be crushed (personal communication, Bristol Myers Squibb Medical Information, March 5, 2009).

Crushing Atripla® tablets: Bioequivalence of Atripla tablet and compounded oral liquid formulation in HIV-negative volunteers was not demonstrated. The 90% CI for FTC Cmax and AUC fell within the range of 0.8-1.25 thus, bioequivalence was met, but the 90% CI for efavirenz Cmax fell below the range of

	bioequivalence while efavirenz AUC∞ fell slightly above the range and tenofovir Cmax and AUC∞ fell above the range. Tenofovir Cmax and AUC∞ were approximately 40% and 20% higher, respectively with the liquid formulation. The clinical implications of these data are unknown.[King et al. JAIDS 2011;56(5):e131-2].
Adjust in Liver Dysfunction	Efavirenz and Atripla® are not recommended in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) because of insufficient data. Caution should be exercised in administering efavirenz or Atripla® to patients with mild hepatic impairment because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience. Limited data available. In 10 volunteers with chronic liver disease, efavirenz Cmax was significantly lower compared to healthy volunteers (3.72 +/- 1.22 uM vs. 5.74 +/- 1.14 uM, respectively) while half-life was longer (152 +/- 41 h vs. 118 +/- 46 h, respectively). There were no significant differences in efavirenz AUC between the two groups (299 +/- 109 uM.h and 305 +/- 124 uM.h in the chronic liver disease and healthy volunteer subjects, respectively).(Fiske et al. CROI 99, #367). A case report documents elevated efavirenz and nelfinavir concentrations in 2 subjects with hepatic impairment, compared to controls (Maserati et al. 1999). Use with caution in patients with impaired hepatic function. Dosage adjustment may be required. In a case control study, HIV-positive subjects with hepatitis B or C coinfection and mild hepatic dysfunction (Child-Pugh score 5-6) did not experience significant differences in efavirenz levels over 2 years compared to a matched HIV-monoinfected control group.(Pereira et al. 2007)
Adjust in Renal Failure/Dialysis	Efavirenz: No adjustment necessary in end-stage renal disease. Atripla®: Because Atripla® is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate to severe renal impairment (creatinine clearance <50 mL/min). Hemodialysis: Hemodialysis does not affect pharmacokinetics of efavirenz. In a prospective study of HIV-infected patients on hemodialysis taking efavirenz 600 mg QD (n=13), 24-hour PK was assessed. Mean Cmin, Cmax, and AUC of EFV was 1.81 mg/mL, 5.04 mg/mL and 71.5 mg h/mL, respectively for efavirenz. The AUC geometric mean ratio (90% CI) was 132% (89, 197). Efavirenz may be administered regardless of hemodialysis schedule because of its extensive hepatic metabolism.[Gupta et al. 2008] CAPD: impact of CAPD on efavirenz removal seems to be minimal. No dosage adjustment required.
Toxicity	**Rash** (26%): usually grade 1/2, can often treat through. Grade

	3/4 rash (1%) . SJS (0.1%). Median time to onset 11 days, median duration 14 days. Mild rash treated symptomatically with antihistamines, analgesics/NSAIDs. **Discontinue** drug if severe rash or rash with constitutional symptoms (fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, lymphadenopathy, increased LFTs or general malaise), and **do not rechallenge**. Avoid use of other NNRITs with history of severe rash to efavirenz. **CNS** (52%): dizziness, impaired concentration, somnolence, abnormal dreams, insomnia, confusion, agitation, depersonalization, amnesia, hallucinations, euphoria. Symptoms usually resolve within a few weeks without interrupting therapy, and may be minimized by bedtime dosing (2.6% discontinuation rate). Worsening of underlying mental illnesses and increased suicidal ideation has been observed. **Other:** teratogenic in monkeys, increased AST/ALT, false-positive cannabinoid test, nausea, vomiting, diarrhea, headache
Pregnancy & Lactation	**Pregnancy risk category D.** Teratogenic effects (i.e. anencephaly, anophthalmia, cleft palate) seen in 3/20 (15%) of monkeys at efavirenz exposures similar to those seen in humans. There are 3 case reports of neural tube defects and 1 case of Dandy Walker Syndrome in humans with first trimester drug exposure. Use of efavirenz is contraindicated in the first trimester of pregnancy. Use after the 2nd trimester can be considered only if there are no other alternatives. Adequate contraception should be used post-partum and in all females of childbearing age. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. NB: current treatment guidelines (DHHS, BHIVA) recommend avoiding use of efavirenz in pregnancy, but state that if a woman conceives while on efavirenz-based therapy and is virally suppressed, efavirenz may be continued. Check most current version of guidelines as information continues to evolve. Antiretroviral Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to efavirenz: 1-800-258-4263. Studies in rats have shown that efavirenz is excreted in milk. Efavirenz concentrations were measured in 34 exclusively-breastfed infants whose mothers were on efavirenz-based regimens. All infants achieved concentrations above the published IC50 for wild-type HIV-1 (0.51ng/ml) and the median concentration was 167 x IC50.(Olagunju et al. CROI 2013)
Drug Interactions	Efavirenz can either induce or inhibit CYP3A4. Also inhibits 2C9, 2C19. Efavirenz induces UGT1A1. See NNRTI interaction chart
Baseline Assessment	Psychiatric assessment (depression, sleep patterns, any CNS disturbances), pregnancy status and adequate contraception in females of childbearing age, CBC/diff, LFTs, examine skin for baseline.

Routine Labs	Psychiatric assessment ,CBC/diff, LFTs q3-6mo. Assess for skin rash and CNS effects every 1-2 weeks when starting therapy for the first 6 weeks. **D/C drug**: LFTs >5xULN, severe rash or rash with constitutional symptoms (see above under toxicity).
Dosage Forms	**Capsules:** • 600 mg (yellow), DIN 02246045 (30 tablets/bottle) • 200 mg (gold), DIN 02239888 (90 capsules/bottle) • 100 mg (white), DIN 02239887 (30 capsules/bottle) • 50 mg (gold and white), DIN 02239886 (30 capsules/bottle) **Pediatric Suspension** (strawberry-mint flavour) available via Expanded Access (1-877-372-7097). **Combination formulations:** • Atripla®: efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg tablet (DIN 02300699)
Storage	Efavirenz capsules and tablets should be stored at 25°C (77°F). Store suspension at room temperature.

References:

Best B et al. 16th Conference on Retroviruses and Opportunistic Infections, February 8-11, 2009, Montreal. Abstract 702.

Bristol-Myers Squibb Canada. Sustiva Product Monograph. Montreal, QC. June 11, 2012.

Fiske W, Benedek I, Brennan J, Davidson A, Gillette S, Joseph J, Kornhauser D. Pharmacokinetics of efavirenz in subjects with chronic liver disease. *Conf Retroviruses Opportunistic Infect*. 1999 Jan 31-Feb 4;6th:137 (abstract no. 367).

Gill MJ, Ostrop NJ, Fiske WD, Brennan JM. Efavirenz dosing in patients receiving continuous ambulatory peritoneal dialysis. *AIDS*. 2000 May 26;14(8):1062-4.

Gupta S, Rosenkranz S, Cramer Y, Koletar S, et al. The pharmacokinetics and pharmacogenomics of efavirenz and lopinavir/ritonavir in HIV-infected persons requiring hemodialysis. AIDS 2008;22:1919–1927.

Izzedine H, Aymard G, Launay-Vacher V, Hamani A, Deray G. Pharmacokinetics of efavirenz in a patient on maintenance haemodialysis. AIDS 2000;14(5):618-9.

Kiser J, McCall M, Cannella A, Markiewicz MA, James A, Acosta EP. Assessment of bioequivalence of tenofovir, emtricitabine and efavirenz (Atripla) fixed dose combination tablet compared with a compounded oral liquid formulation derived from the tablet [abstract 605]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Letendre S, Ellis RJ, Deutsch R, Clifford DB, Collier AC, Gelman GG, et al. Correlates of time-to-loss-of-viral-response in CSF and plasma in the CHARTER Cohort [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

Maserati R, Villani P, Seminari E, Pan A, Lo Caputo S, Regazzi MB. High plasma levels of nelfinavir and efavirenz in two HIV-positive patients with hepatic disease. AIDS. 1999 May 7;13(7):870-1

Olagunju A, Amara A, Rjia J, et al. Exposure of breastfed infants to maternal efavirenz from breast milk

[abstract 933]. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, March 3-6, 2013.
http://www.retroconference.org/2013b/Abstracts/45857.htm

Pereira S, Caixas U, Branco T, Germano I, Lampreia F, Azuaje C et al. Does HCV or HBV infection influence efavirenz plasma concentrations in HIV-infected patients with well compensated disease? [abstract 3]. 8th International Workshop on Clinical Pharmacology of HIV Therapy. Budapest, Hungary, April 16-18, 2007.

Yilmaz A, Watson V, Dickinson L, Back D. Efavirenz pharmacokinetics in cerebrospinal fluid and plasma over a 24-hour dosing interval. Antimicrob Agents Chemother 2012;56 4583-4585.