Selected Properties of Nelfinavir

Other names	Viracept®
Manufacturer	Pfizer Canada Inc.
Pharmacology/Mechanism of Action	HIV aspartic protease is critical in the post-translational processing of the polyprotein products of gag and gag-pol genes into the functional core proteins and viral enzymes. Inhibition of viral protease prevents cleavage of the gag-pol polyprotein thus producing immature, non-infectious virions.
Activity	The EC95 (95% effective concentration) of nelfinavir ranged from 7 to 196 NM in vitro. WT IC50: 0.0015-0.0094 uM (Phenosense) In vitro - synergistic activity with AZT, 3TC, ddC, additive with ddI, d4T
Resistance - genotypic	Mutations in the protease gene associated with resistance to protease inhibitors (IAS-USA Fall 2005 Resistance Mutations): Major: D30N, L90M Minor: L10F/I, M36I, M46I/L, A71V/T, V77I, V82A/F/T/S, I84V, N88D/S *as major & minor mutations accumulate, susceptibility to PIs decreases*
Resistance - phenotypic	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ (http://hivdb.stanford.edu/): D30N: 14-fold ↑ (intermediate resistance) D30N, N88D: 52-fold ↑ (high resistance) 84V, 90M: 18-fold ↑ (high resistance)
Cross-Resistance	Most patient-derived recombinant isolates with phenotypic and genotypic evidence of reduced susceptibility (>2.5-fold) to amprenavir, indinavir, lopinavir, and/or saquinavir demonstrated high-level cross-resistance to nelfinavir, *in vitro.* Mutations associated with resistance to other PIs (e.g. G48V, V82A/F/T, I84V, L90M) appeared to confer high-level cross-resistance to NFV.
Oral Bioavailability	F= good (20% monkeys, 52-80% rats) NB: 625 mg tablet • Pfizer (Agouron) product: similar excipients, ↑ bioavailability, possibly ↑ diarrhea vs. 250 mg tablet • Roche product: different excipients, equivalent bioavailability, ↓ diarrhea vs. 250 mg tablet
Effect of Food	Food ↑ AUC by 2-3 times and decreases nelfinavir pharmacokinetic variability relative to the fasted state. **Changes in AUC, C_{max} and T_{max} for Nelfinavir in Fed State Relative to Fasted State Following 1250 mg VIRACEPT (5 x 250 mg tablets)** Number of Kcal / % Fat / Number of subjects / AUC fold increase / C_{max} fold increase / Increase in T_{max} (hr) 125 / 20 / n=21 / 2.2 / 2.0 / 1.00 500 / 20 / n=22 / 3.1 / 2.3 / 2.00 1000 / 50 / n=23 / 5.2 / 3.3 / 2.00

Protein Binding	>98% (98% AAG, 98% albumin)
Vd	2-7 L/kg
Tmax	2-4 hours (with food)
serum T ½	3.5-5 hours
Drug Concentrations	Steady-state plasma nelfinavir concentrations: 1250 mg BID (five 250 mg tablets): AUC24 52.8 ± 15.7 mg.h/L, Cmax 4.0 ± 0.8 mg/L, Ctrough morning 2.2 ± 1.3 mg/L, Ctrough evening 0.7 ± 0.4 mg/L 750 mg TID: AUC24 43.6 ± 17.8 mg.h/L, Cmax 3.0 ± 1.6 mg/L, Ctrough morning 1.4 ± 0.6 mg/L, Ctrough evening 1.0 ± 0.5 mg/L NB: Dosing with the 625 mg tablet yields 24% ↑ AUC, similar Cmax compared to the 250 mg tablets under fed conditions. In vivo intracellular accumulation: cell/plasma ratio 2.7-5.3 (nelfinavir alone), 2.3 (M8 metabolite)
Minimum target trough concentrations (for wildtype virus)	0.8 mg/mL
CSF (% of serum)	In the rat model, penetration noted; brain levels 40-fold higher than required for antiviral activity. 2010 CNS Penetration Effectiveness (CPE) Score: 1 [Letendre S et al. 2010]
Metabolism	Metabolized by CYP3A4 and CYP2C19. Inhibitor of CYP3A4. Induces CYP2B6, 2C8 and 2C9. The major oxidative metabolite (M8) has *in vitro* antiviral activity equal to the parent drug.
Excretion	-87% biliary/ fecal (78% as oxidative metabolites) -<2% renal
Dosing – Adult	**750 mg po TID or 1250 mg po BID.** Doses of 1500 mg BID are under study. **Take with a meal to increase absorption.**
Dosing – Pediatric	**Neonate** (<6 weeks) PACTG 353: [Bryson et al, 2002] *Protocol Dose*: 40 mg/kg/dose po bid (28% of infants were sub-therapeutic at this dose and higher doses of 50-55 mg/kg/dose po q12h under investigation). **Pediatric (2 to 13 years old)**: 50 mg/kg/dose po BID; range 45-55 mg/kg/dose po BID. Use multiples of 50 mg for powder or solubilized tablets. **Investigational (> 6 y.o.)**: 50-55 mg/kg/dose po bid
Special instructions for pediatric patients	**Tablets:** **-** both 250 mg and 625 mg tablets can be crushed and dispersed or added to food - Tablet dispersion: Use 250 mg tablet in 5 mL sterile water to yield a 50 mg/mL dispersion. Use syringe with 1 mL increments to measure. Round dose to nearest 50mg. - dispersed tabs can be added to milk or chocolate milk

	- crushed tabs can be added to pudding or other foods - due to bitter taste, avoid mixing with acidic food or juice (orange juice, apple juice, applesauce) - tablet or powder mixed with food or liquid is stable for 6 hours (refrigerated) **Powder:** - measure out powder & mix with water, milk, formula, pudding, ice cream, chocolate milk. Mix well as drug will settle. - powder has gritty & thick texture (G-tube blockage with powder or dissolved tablet) Do not reconstitute in original container–use special scoop.
Adjust in Liver Dysfunction	Nelfinavir pharmacokinetics were assessed in five HIV-positive patients with hepatitis C and liver disease.[Khaliq et al, 2000] Investigators found nelfinavir dosage adjustment to be useful in 2 patients with severe proven liver disease (i.e., AST, ALT 11-16 times upper limit of normal, ULN). Dosage reduction was not necessary in the remaining patients (AST <3-4 x ULN, ALT <4-12 x ULN). Manufacturer does not have specific dosage recommendations in hepatic impairment.
Adjust in Renal Failure/Dialysis	Dosage adjustment not required (<2% renal excretion). Dosage adjustments do not appear to be necessary in CAPD (Taylor et al. 2000).
Toxicity	**GI:** diarrhea (common), nausea, abdominal pain, flatulence **Hepatic:** ↑ LFTs , exacerbation of chronic liver disease **Derm:** rash **Other:** Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat malditribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.
Pregnancy & Lactation	Pregnancy risk category B. Minimal placental passage. 1250 mg BID is recommended dose (750 mg TID may yield subtherapeutic concentrations). Standard 1250 mg BID dosing in pregnancy shown to result in 31% ↓ nelfinavir AUC and 75% ↓ M8 AUC during the 3rd trimester vs. post-partum. In a multi-center, ongoing, prospective study, nelfinavir pharmacokinetics were compared in women receiving 1875 mg BID vs. 1250 mg BID during the 3rd trimester. The 1875 mg BID dose during the 3rd trimester was found to achieve nelfinavir and M8 exposures comparable to the standard nelfinavir dose of 1250 mg BID postpartum.[McCormack S et al. 2014 IWCPHT] NB: Health Canada advises against using nelfinavir in pregnant women due to safety concerns regarding ethyl methanesulfonate during pregnancy (Health Canada Advisory, August 21, 2008. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_144-eng.php) Note that this is in contrast to the FDA, which removed its warning of process-related impurity with nelfinavir in May 2008, allowing nelfinavir to be prescribed as indicated to all patient populations (including children and pregnant women).

	http://aidsinfo.nih.gov/contentfiles/NFV_prescribing_info.pdf In 7 HIV-infected pregnant women receiving nelfinavir (all VL<40 copies/mL at delivery), mean nelfinavir cord:mother blood concentration ratio was 0.42 (SD +/- 0.27); cord blood concentrations were below cut-off values in 3 (42.8%) of samples. Undetectable viral load was found in amniotic fluid and cord blood.[Ivanovic et al. 2010].
Drug Interactions	Nelfinavir is an inhibitor of CYP3A4. See Separate Drug Interaction Table
Baseline Assessment	Assess risk factors for diabetes, coronary artery disease, osteonecrosis (i.e. steroids, ETOH, diabetes, hyperlipidemia), and hepatic dysfunction (i.e. HBV/HCV, ETOH use). CBC/diff, LFTs, glucose, fasting cholesterol profile, underlying diarrhea.
Routine Labs	CBC/diff, LFTs, glucose q 3 mos. Fasting lipids (8-12 hr level) q 3-6 months post-therapy, then annually. If TG > 2.3 mmol/L at baseline, repeat after 1-2 months. Assess for diarrhea, nausea.
Dosage Forms	**Tabs:** 250mg (light blue); DIN 02238617 625mg (white oval);DIN 02248761 **Powder:** 50mg/g (1g= level scoopful); DIN 02238618 *oral powder discontinued 2006
Storage	Store tablets at room temperature.

References:

Pfizer Canada Inc. Viracept Product Monograph. Kirkland QC. March 4, 2011.

Bryson Y, Stek A, Mirochnick M, Mofenson L, Connor J, Watts H, Huang S, et al. Pharmacokinetics, antiviral activity, and safetly of nelfinavir (NFV) with ZDV/3TC in pregnant HIV-infected women and their infants: PACTG 353 cohort 2 [abstract 795-W]. 9th Conference on Retroviruses and Opportunistic Infections. Seattle, Washington, February 24-28, 2002.

Dixit V, Hariparsad N, Li F, Desai P, Thummel KE, Unadkat JD. Cytochrome P450 enzymes and transporters induced by anti-human immunodeficiency virus protease inhibitors in human hepatocytes: implications for predicting clinical drug interactions. Drug Metab Disposition 2007;35:1853-9.

Ford J, Khoo SH, Back DJ. The intracellular pharmacology of antiretroviral protease inhibitors. JAC 2004 (advance on-line publication).

Ivanovic J, Nicastri E, Viscione M, Bellagamba R, Signore F, Pisani G et al. Cord blood and amniotic fluid exposures of protease inhibitors and viral load quantification in HIV-infected pregnant women [abstract WEPE0100]. XVIII International AIDS Conference, Vienna, Austria, July 18-23rd, 2010.

Khaliq Y, Gallicano K, Seguin I, Fyke K, Carignan G, Bulman D, Badley A, Cameron DW. Single and multiple dose pharmacokinetics of nelfinavir and CYP2C19 activity in human immunodeficiency virus-infected patients with chronic liver disease. Br J Clin Pharmacol. 2000 Aug;50(2):108-15.

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: CPE score predicts CSF suppression [abstract 430]. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, CA, February 16-19, 2010.

McCormack SA, Best BM, Stek A, et al. Pharmacokinetics of an increased nelfinavir dose during the third trimester of pregnancy [abstract P_38]. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, Washington DC, May 19-21, 2014.

Taylor S, Little J, Halifax K, Drake S, Back D. Pharmacokinetics of nelfinavir and nevirapine in a patient with end-stage renal failure on continuous ambulatory peritoneal dialysis. J Antimicrob Chemother. 2000 May;45(5):716-7.

