

### Selected Properties of Nelfinavir

<b>Other names</b>	Viracept®
<b>Manufacturer</b>	Pfizer Canada Inc.
<b>Pharmacology/Mechanism of Action</b>	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.
<b>Activity</b>	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
<b>Resistance - genotypic</b>	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  <i>* as major &amp; minor mutations accumulate, susceptibility to PIs decreases</i>
<b>Resistance - phenotypic</b>	Phenotypic data on clinical virus isolates associated with various mutations using ViroLogic PhenoSense™ ( <a href="http://hivdb.stanford.edu/">http://hivdb.stanford.edu/</a> ): D30N: 14-fold ↑ (intermediate resistance) D30N, N88D: 52-fold ↑ (high resistance) 84V, 90M: 18-fold ↑ (high resistance)
<b>Cross-Resistance</b>	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, <i>in vitro</i> . Mutations associated with resistance to other PIs (e.g. G48V, V82A/F/T, I84V, L90M) appeared to confer high-level cross-resistance to NFV.

<b>Oral Bioavailability</b>	<p>F= good (20% monkeys, 52-80% rats)  NB: 625 mg tablet</p> <ul style="list-style-type: none"> <li>• Pfizer (Agouron) product: similar excipients, ↑ bioavailability, possibly ↑ diarrhea vs. 250 mg tablet</li> <li>• Roche product: different excipients, equivalent bioavailability, ↓ diarrhea vs. 250 mg tablet</li> </ul>																								
<b>Effect of Food</b>	<p>Food ↑ AUC by 2-3 times and decreases nelfinavir pharmacokinetic variability relative to the fasted state.</p> <p>Changes in AUC, C<sub>max</sub> and T<sub>max</sub> for Nelfinavir in Fed State Relative to Fasted State Following 1250 mg VIRACEPT (5 x 250 mg tablets)</p> <table border="1"> <thead> <tr> <th>Number of Kcal</th> <th>% Fat</th> <th>Number of subjects</th> <th>AUC fold increase</th> <th>C<sub>max</sub> fold increase</th> <th>Increase in T<sub>max</sub> (hr)</th> </tr> </thead> <tbody> <tr> <td>125</td> <td>20</td> <td>n=21</td> <td>2.2</td> <td>2.0</td> <td>1.00</td> </tr> <tr> <td>500</td> <td>20</td> <td>n=22</td> <td>3.1</td> <td>2.3</td> <td>2.00</td> </tr> <tr> <td>1000</td> <td>50</td> <td>n=23</td> <td>5.2</td> <td>3.3</td> <td>2.00</td> </tr> </tbody> </table>	Number of Kcal	% Fat	Number of subjects	AUC fold increase	C <sub>max</sub> fold increase	Increase in T <sub>max</sub> (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
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<b>Protein Binding</b>	>98% (98% AAG, 98% albumin)																								
<b>Vd</b>	2-7 L/kg																								
<b>Tmax</b>	2-4 hours (with food)																								
<b>serum T<sub>1/2</sub></b>	3.5-5 hours																								
<b>Drug Concentrations</b>	<p>Steady-state plasma nelfinavir concentrations:</p> <p><u>1250 mg BID (five 250 mg tablets):</u>  AUC<sub>24</sub> 52.8 ± 15.7 mg.h/L, C<sub>max</sub> 4.0 ± 0.8 mg/L, C<sub>trough</sub> morning 2.2 ± 1.3 mg/L, C<sub>trough</sub> evening 0.7 ± 0.4 mg/L</p> <p><u>750 mg TID:</u>  AUC<sub>24</sub> 43.6 ± 17.8 mg.h/L, C<sub>max</sub> 3.0 ± 1.6 mg/L, C<sub>trough</sub> morning 1.4 ± 0.6 mg/L, C<sub>trough</sub> evening 1.0 ± 0.5 mg/L</p> <p>NB: Dosing with the 625 mg tablet yields 24% ↑ AUC, similar C<sub>max</sub> compared to the 250 mg tablets under fed conditions.</p> <p>In vivo intracellular accumulation: cell/plasma ratio 2.7-5.3 (nelfinavir alone), 2.3 (M8 metabolite)</p>																								
<b>Minimum target trough concentrations (for wildtype virus)</b>	0.8 mg/mL																								
<b>CSF (% of serum)</b>	In the rat model, penetration noted; brain levels 40-fold higher than required for antiviral activity																								
<b>Metabolism</b>	<p>Nelfinavir inhibits CYP3A4.</p> <p>Metabolized via CYP3A4 &gt;&gt; CYP2C19, CYP2D6 and CYP2C9.</p> <p>Activity of major oxidative metabolite (M1) has antiviral activity (10 x less than parent).</p>																								

<b>Excretion</b>	-87% biliary/ fecal (78% as oxidative metabolites) -<2% renal
<b>Dosing – Adult</b>	<b>750 mg po TID or 1250 mg po BID.</b> Doses of 1500 mg BID are under study. <b>Take with a meal to increase absorption.</b>
<b>Dosing – Pediatric</b>	<b>Neonate (&lt;6 weeks) PACTG 353:</b> [Bryson et al, 2002] <i>Protocol Dose:</i> 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).  <b>Pediatric (2 to 13 years old):</b> 50 mg/kg/dose po BID; range 45-55 mg/kg/dose po BID. Use multiples of 50 mg for powder or solubilized tablets.  <b>Investigational (&gt; 6 y.o.):</b> 50-55 mg/kg/dose po bid
<b>Special instructions for pediatric patients</b>	<b>Tablets:</b> - 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)  <b>Powder:</b> - 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.
<b>Adjust in Liver Dysfunction</b>	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.

<b>Adjust in Renal Failure/Dialysis</b>	Dosage adjustment not required (<2% renal excretion). Dosage adjustments do not appear to be necessary in CAPD (Taylor et al. 2000).
<b>Toxicity</b>	<b>GI:</b> diarrhea (common), nausea, abdominal pain, flatulence <b>Hepatic:</b> ↑ LFTs , exacerbation of chronic liver disease <b>Derm:</b> rash <b>Other:</b> Protease class effects include: hyperlipidemia, hypertriglyceridemia, hyperglycemia, fat maldistribution, weight gain, increase in LFTs, hepatitis, increased bleeding in hemophiliacs, osteonecrosis.
<b>Pregnancy &amp; Lactation</b>	Pregnancy risk category B. Minimal placental passage. 1250 mg BID is recommended dose (750 mg TID may yield subtherapeutic concentrations).
<b>Drug Interactions</b>	Nelfinavir is an inhibitor of CYP3A4. See Separate Drug Interaction Table
<b>Baseline Assessment</b>	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.
<b>Routine Labs</b>	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.
<b>Dosage Forms</b>	<b>Tabs:</b> 250mg (light blue); DIN 02238617 625mg (white oval);DIN 022408761 <b>Powder:</b> 50mg/g (1g= level scoopful); DIN 02238618 <b>*oral powder discontinued 2006</b>
<b>Storage</b>	Store tablets at room temperature.

## References:

### Pfizer Canada Inc. Viracept Product Monograph. Kirkland QC: 2003.

PACTG 353 Reference

Bryson Y, Stek A, Mirochnick M, Mofenson L, Connor J, Watts H, Huang S, et al. Pharmacokinetics, antiviral activity, and safety 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.

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

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.

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.