### Selected Properties of Nelfinavir

<table>
<thead>
<tr>
<th>Other names</th>
<th>Viracept®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Pfizer Canada Inc.</td>
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</tbody>
</table>

#### 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.

<table>
<thead>
<tr>
<th>Number of Kcal</th>
<th>% Fat</th>
<th>Number of subjects</th>
<th>AUC fold increase</th>
<th>Cmax fold increase</th>
<th>Increase in Tmax (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>30</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>5.3</td>
<td>2.00</td>
</tr>
</tbody>
</table>
## 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

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Steady-state Plasma Nelfinavir Concentrations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1250 mg BID (five 250 mg tablets):</td>
<td>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</td>
</tr>
<tr>
<td>750 mg TID:</td>
<td>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</td>
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</table>

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
- 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

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Protocol Dose</th>
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<tbody>
<tr>
<td>Neonate (&lt;6 weeks)</td>
<td>40 mg/kg/dose po bid (28% of infants were subtherapeutic at this dose and higher doses of 50-55 mg/kg/dose po q12h under investigation).</td>
</tr>
<tr>
<td>Pediatric (2 to 13 years old):</td>
<td>50 mg/kg/dose po BID; range 45-55 mg/kg/dose po BID. Use multiples of 50 mg for powder or solubilized tablets.</td>
</tr>
<tr>
<td>Investigational (&gt; 6 y.o.):</td>
<td>50-55 mg/kg/dose po bid</td>
</tr>
</tbody>
</table>

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