

### Selected Properties of Nevirapine

<b>Other names</b>	Viramune®, Viramune XR®, Auro-Nevirapine®
<b>Manufacturer</b>	Boehringer Ingelheim (Canada) Ltd., Aurobindo Pharma Limited
<b>Pharmacology/Mechanism of Action</b>	Dipyridodiazepinone derivative, considered a TIBO (tetrahydroimidazobenzodiazepinone) -like compound, and structurally related to benzodiazepines. 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.
<b>Activity</b>	IC50: 10-100 nM against laboratory and clinical isolates of HIV-1
<b>Resistance - genotypic</b>	Mutations in the reverse transcriptase gene associated with resistance to reverse transcriptase inhibitors (IAS-USA Fall 2005 Resistance Mutations): <i>L100I<sup>#</sup>, K103N*, V106A/M*<sup>#</sup>, V108I, Y181C/I<sup>#</sup>, Y188C/L/H*, G190A<sup>#</sup></i> <b>*multi-NNRTI resistance</b> <i><sup>#</sup>accumulation of ≥2 leads to multi-NNRTI resistance</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> ) WT IC50: 0.046-0.286 uM (Phenosense) K103N: 47-fold ↑ (high resistance) V106A: 64-fold ↑ (high resistance) Y181C/I: 85-fold ↑ (high resistance) Y188L: 450-fold ↑ (high resistance) Y188C/H: intermediate to high-level resistance G190A: 75-fold ↑ (high-level resistance) L100I + K103N: 78-fold ↑ (high resistance) K103N+Y181C: 400-fold ↑ (high resistance)
<b>Cross-Resistance</b>	Rapid emergence of HIV strains that are cross-resistant to NNRTIs observed in vitro. Cross-resistance between nevirapine and protease inhibitors or nucleoside analogues unlikely because enzyme targets are different.
<b>Oral Bioavailability</b>	>90%
<b>Effect of Food</b>	No effect of food. Can take with or without food.
<b>Protein Binding</b>	60%
<b>Vd</b>	Nevirapine is highly lipophilic; Vd 1.21 +/- 0.09 L/kg (following IV dose).  In one phase I study in healthy volunteers, the weight-adjusted apparent volume of distribution (Vdss/F) was higher in women vs. men (1.54 vs. 1.38 L/kg), but this was offset by a shorter terminal t1/2 in women, resulting in no overall difference in nevirapine clearance between genders.

<b>Tmax</b>	2 hours
<b>serum T ½</b>	25-30 hours
<b>Drug Concentrations</b>	<p>Cmax (4 hours after single 200 mg dose): 2 ± 0.4 ug/mL (7.5 uM);</p> <p>At dose of 400 mg/day (n=242), Cmin at steady state: 4.5 ± 1.9 ug/mL (17 ± 7 uM).</p> <p>In 108 patients on a nevirapine-based regimen, median nevirapine Ctrough was 5624 ± 1812 vs. 4468 ± 1568 ng/mL in individuals with mutant allele (GT or TT, n=54) for CYP2B6 516 as compared to individuals with wild-type genotype (GG, n=54), p=0.001. The combined effect of additional SNPs ABCB1 3435C&gt;T and 1236 C&gt;T yielded a significant positive correlation with nevirapine Ctrough.[D'Avolio et al. 2010]</p> <p>Nevirapine concentrations were measured in paired plasma and stimulated saliva samples from 297 Ugandan, HIV-infected adults receiving nevirapine-based cART. Median nevirapine concentrations in saliva and plasma were 3.40 and 6.12 mg/L, respectively. The mean saliva:plasma ratio was 0.55 (62% CV).[Lamorde et al. 2013]</p>
<b>Minimum target trough concentrations (for wildtype virus)</b>	<p>3.4 mg/mL</p> <p>4.30 mg/mL may be associated with lower probability of selection of nevirapine-associated primary resistance mutations in case of virologic failure.</p>
<b>CSF (% of serum)</b>	<p>45% (equal to unbound drug)</p> <p>2010 CNS Penetration Effectiveness (CPE) Score: 4 [Letendre S et al. 2010]</p>
<b>Metabolism</b>	>95% metabolism via P450 3A4 oxidation, and 2B6 to a minor extent, followed by biliary excretion.
<b>Excretion</b>	hydroxylated metabolites excreted in urine; <3% total dose excreted unchanged. Nevirapine is metabolized more quickly in pediatric patients vs. adults.

<p><b>Dosing – Adult</b></p>	<p>200mg po once daily for 14 days (lead in), followed by 200 mg bid (immediate-release tablets) or 400 mg once daily (extended release tablet)</p> <p>Extended-release (400 mg XR) tablets must be swallowed whole; they must not be chewed, crushed or divided.</p> <p><b>NB: avoid use in women with CD4 &gt;250 (12-fold ↑ risk) and in men with CD4 &gt;400 (3-fold ↑ risk) due to increased risk of symptomatic hepatotoxicity.</b></p> <p><b>If switching from efavirenz to nevirapine</b> (e.g., for CNS-related side effects), may use either standard nevirapine lead-in period or full BID dosing right away. In 39 patients on an efavirenz-based regimen with CNS toxicity, subjects were randomized to switch to nevirapine with either lead-in dosing or full dosing immediately. A higher percentage of patients in the full-dose arm achieved therapeutic nevirapine levels &gt;3 ug/mL versus the lead-in dosing group (89 vs 44% at day 7, p=0.006, 82 vs 32% at day 14, p=0.003), but there was a trend to higher incidence of rash and hepatic toxicity in the full-dose arm. Rash was related to nevirapine plasma levels at day 7 (6.6 vs. 3.6 ug/mL in patients with or without rash, p=0.007). Of note, efavirenz plasma concentrations remained detectable after 14 days without differences in treatment arms.[Ribera et al. 2010]</p>
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<p><b>Dosing – Pediatric</b></p>	<p><b>Pediatric</b><sup>1</sup>: 150 mg/m<sup>2</sup>/dose po once daily for 14 days, then 150 mg/m<sup>2</sup>/dose po bid range: 120-200 mg/m<sup>2</sup>/dose bid if no rash or ADR <b>Neonate</b> (&lt;3 months) (PACTG 365): 5 mg/kg/dose po once daily OR 120 mg/m<sup>2</sup>/dose po once daily for 14 days, then 120 mg/m<sup>2</sup>/dose po bid for 14 days, then 200 mg/m<sup>2</sup>/dose po bid <b>Newborn prophylaxis</b>: mother 200 mg po x 1 at onset of labour; baby 2 mg/kg/dose po x 1 at 48-72 hours</p> <p>Pediatric patients may be dosed using VIRAMUNE XR 400 mg or 100 mg tablets. VIRAMUNE XR is dosed based on a patient's body surface area (BSA) calculated using the Mosteller formula. All pediatric patients must initiate therapy with immediate-release VIRAMUNE (as 150 mg/m<sup>2</sup> of VIRAMUNE Oral Suspension or as VIRAMUNE tablets), at a dose not to exceed 200 mg per day, administered once daily for the first 14 days. This lead-in period should be used because it has been demonstrated to reduce the frequency of rash. This lead-in period is not required if the patient is already on a regimen of twice daily immediate-release formulation in combination with other antiretroviral agents.</p> <p>The recommended oral doses of VIRAMUNE XR for pediatric patients 6 to less than 18 years of age based upon their BSA are described in the table below. The total daily dose should not exceed 400 mg for any patient.</p> <p><b>Recommended VIRAMUNE XR Dosing for Pediatric Patients 6 to less than 18 years of age by BSA after the Lead-in Period with Immediate-Release VIRAMUNE</b></p> <table border="1" data-bbox="696 1207 1443 1451"> <thead> <tr> <th>BSA range (m<sup>2</sup>)</th> <th>VIRAMUNE XR tablets dose (mg)</th> </tr> </thead> <tbody> <tr> <td>0.58 - 0.83</td> <td>200 mg once daily (2 x 100 mg)</td> </tr> <tr> <td>0.84 - 1.16</td> <td>300 mg once daily (3 x 100 mg)</td> </tr> <tr> <td>≥1.17</td> <td>400 mg once daily (1 x 400 mg)</td> </tr> </tbody> </table>	BSA range (m <sup>2</sup> )	VIRAMUNE XR tablets dose (mg)	0.58 - 0.83	200 mg once daily (2 x 100 mg)	0.84 - 1.16	300 mg once daily (3 x 100 mg)	≥1.17	400 mg once daily (1 x 400 mg)
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<p><b>Special instructions for pediatric patients</b></p>	<p>May crush immediate-release tablets, mix in water and give orally or by G-tube; liquid formulation available via SAP.</p> <p>Extended-release (400 mg XR) tablets must be swallowed whole; they must not be chewed, crushed or divided.</p>								
<p><b>Adjust in Liver Dysfunction</b></p>	<p>Patients with mild hepatic impairment do not require an adjustment in nevirapine dosing; however, caution should be exercised when nevirapine or nevirapine XR is administered to patients with moderate hepatic impairment. Nevirapine or nevirapine XR should not be administered to patients with severe</p>								

	<p>hepatic dysfunction.[Viramune Product Monograph, 2013]</p> <p>Single-dose pharmacokinetics of nevirapine were assessed in 10 subjects with hepatic impairment, and compared to 8 subjects with normal hepatic function. Mild-moderate hepatic impairment (i.e., Child-Pugh score <math>\leq 7</math>) had no significant effect on nevirapine kinetics. However, potential for nevirapine accumulation in subjects with severe hepatic dysfunction and/or moderate-severe ascites.</p> <p>In a cross-sectional study of nevirapine concentrations in HIV/HCV and HIV infected subjects, median NVP C<sub>min</sub> were similar between the 2 groups, but varied according to fibrosis stage. In co-infected subjects, those with cirrhosis (METAVIR fibrosis stage 4) had significantly higher NVP C<sub>min</sub> compared to the less fibrotic group.[<i>Dominguez et al. 2006</i>] In a prospective study, nevirapine C<sub>trough</sub> concentrations were significantly higher in HIV/HCV co-infected patients (n=9) compared to HIV monoinfected subjects (n=18): median C<sub>trough</sub> 5810 ng/mL vs 4826 ng/mL, respectively.[<i>Dragovic et al. 2007</i>]</p> <p>In a series of 51 HIV-infected patients on chronic nevirapine treatment and who had various degrees of hepatic fibrosis including cirrhosis, trough plasma nevirapine concentrations were not significantly increased according to stage of fibrosis, and thus, no dose adjustment is warranted. [Cammett et al. 2009]</p> <p>Use nevirapine with caution in patients with impaired hepatic function. May consider empiric dosage reduction in significant hepatic dysfunction.</p>
<p><b>Adjust in Renal Failure/Dialysis</b></p>	<p>In End Stage Renal Disease (ESRD) appropriate doses of nevirapine or nevirapine extended-release with respect to safety and efficacy have not been established.</p> <p>In renal dysfunction, a single dose study suggested that patients with a creatinine clearance <math>\geq 20</math> mL/min do not require an adjustment in nevirapine dosing. Nevirapine extended-release tablets have not been studied in patients with renal dysfunction.</p> <p>Single-dose kinetics of nevirapine were assessed in 23 subjects with mild (<math>50 \leq \text{Clcr} &lt; 80</math> mL/min), moderate (<math>30 \leq \text{Clcr} &lt; 50</math> mL/min) or severe (<math>\text{Clcr} &lt; 30</math> mL/min) renal dysfunction or end stage renal disease (ESRD) requiring dialysis, as well as 8 subjects with normal renal function. Nevirapine pharmacokinetics were not changed in any category of renal impairment.</p> <p><u>Hemodialysis:</u> Subjects with ESRD requiring dialysis exhibited a 43.5% reduction in nevirapine AUC over a one week exposure period with an accumulation of nevirapine hydroxy-metabolites in plasma. An additional 200 mg dose of nevirapine immediate-release tablets following each dialysis treatment is recommended in patients requiring dialysis.[Viramune Product Monograph, 2013].</p>

	<p>In 3 HIV-positive subjects on hemodialysis taking nevirapine 200 mg BID, The geometric means of observed nevirapine C<sub>min</sub> were 4.77 and 4.01 mg/mL; and of systemic NVP clearance were 2.72 and 2.84 on nondialysis and dialysis days, respectively. Steady-state pharmacokinetics of NVP given 200 mg twice daily were similar to those in patients without renal failure, and only minimal differences in PK parameters between dialysis and nondialysis days were observed. No dose adjustment of nevirapine is required.[Cramer et al. JAIDS 2010]</p> <p><u>CAPD</u>: no dosage adjustment required.</p>
<b>Toxicity</b>	<p><b>Rash</b>: mild rash+/- pruritus (17%), severe grade3/4 rash (7%), SJS reported; fatality reported due to toxic epidermal necrolysis. Rash minimized by lead-in dosing of 200mg once daily x 14d. If rash occurs, escalation of dose to 200mg bid <b>should not occur</b> until rash resolution. Mild rash treated symptomatically with antihistamines, analgesics/NSAIDs. <b>Discontinue</b> 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 <b>do not rechallenge</b>. Rash typically occurs within first 6 weeks of treatment.</p> <p><b>Hepatic</b>: symptomatic events (4%); higher in women with CD<sub>4</sub> &gt; 250 (11%) and men with CD<sub>4</sub> &gt; 400 (6.3%). ~ 50% of cases accompanied by <b>skin rash</b> (± eosinophilia and systemic symptoms); may progress to fulminant hepatic failure with encephalopathy &amp; fatal necrosis. Often presents with abrupt onset of flu-like symptoms (nausea, vomiting, fatigue, myalgias, abdominal pain, fever). May occur through 18 weeks.</p> <p><b>Other, &gt;5%</b>: fever, headache, somnolence, nausea, elevated GGT. .</p>
<b>Pregnancy &amp; Lactation</b>	<p>Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is pregnancy category C. Caution warranted (especially with CD<sub>4</sub> count &gt; 250) since cases of severe and fatal hepatotoxicity often associated with rash have been reported in the first 6 weeks. Monitor closely for the first 18 weeks. Call 1-866-234-2345 to report ADRs.</p> <p>In a prospective pharmacokinetic study of Ugandan women receiving nevirapine-based therapy during pregnancy, intensive PK sampling was undertaken between weeks 20-24, 32-36 and six weeks post-partum. Nevirapine exposures were reduced approximately 20% during the 3<sup>rd</sup> trimester compared to post-partum. Adequate viral suppression was maintained in all patients.[Lamorde et al. 2010]</p>
<b>Drug Interactions</b>	<p>Nevirapine primarily induces enzymes of P450 3A. See NNRTI interaction chart.</p>
<b>Baseline Assessment</b>	<p>CBC/diff, LFTs, examine skin for baseline. Risk factors for hepatotoxicity: higher CD4 count, female, pregnancy, elevated baseline ALT or AST, HBV or HCV co-infection, alcoholic liver, HIV (-) when used for PEP.</p>

<b>Routine Labs</b>	Monitor LFTs (every 2 weeks x 1 month, then monthly x 3 months, then every 3 months). CBC/diff q3-6mo. Assess for skin rash (most common in 1st 6 weeks of therapy). <b>D/C drug:</b> LFTs >5xULN, hepatitis, severe rash or rash with constitutional symptoms (see above under toxicity).
<b>Dosage Forms</b>	200mg (white) tablets (DIN 02238748) 200 mg tablets (generic): DIN 02318601, 02387727, 02352893 10mg/mL syrup; 240 mL bottle via SAP (ph: 613-941-2108) 400 mg extended release tablets (DIN 02367289) 100 mg extended release tablets (available in US)
<b>Storage</b>	Store tablets and liquid at room temperature (15-30°C).

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