

Nevirapine

Brand Name: Viramune

Drug Class: Non-nucleoside Reverse Transcriptase Inhibitors

Drug Description

Nevirapine is a dipyrindodiazepine derivative non-nucleoside reverse transcriptase inhibitor (NNRTI). [1]

HIV/AIDS-Related Uses

Nevirapine was approved by the FDA on June 21, 1996, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.[2] Nevirapine is approved for use in adults and in pediatric patients 15 days and older.[3]

Administration of single-dose nevirapine to the mother intrapartum and to the infant postpartum effectively reduces vertical transmission of HIV-1.[4] This regimen, recommended only for use in HIV-infected treatment-naïve women in labor who have had no prior therapy for HIV, includes a single nevirapine dose given to the mother at the onset of labor and a single nevirapine dose given to the neonate 48 to 72 hours after birth.[5]

Pharmacology

Nevirapine exerts a virustatic effect by acting as a specific, noncompetitive HIV-1 reverse transcriptase (RT) inhibitor. The drug binds directly to heterodimeric HIV-1 RT and appears to inhibit RT activity by disrupting the catalytic site of the enzyme. Nevirapine has a very limited spectrum of antiviral activity. The drug has in vitro virustatic activity against HIV-1, but is inactive against HIV-2 and animal retroviruses.[6]

Nevirapine is more than 90% absorbed after oral administration in healthy adults and adults with HIV-1 infection. Absolute bioavailability in a trial of 12 healthy adults following single-dose administration was 93% for a 50 mg oral tablet and 91% for 5 ml (nevirapine hemihydrate 50 mg) of oral suspension. When nevirapine was administered to 24 healthy adults with either a high-fat breakfast or an antacid, the extent of absorption was comparable to that seen under fasting conditions.[7]

Although distribution of nevirapine into body

tissues and fluids has not been fully characterized, animal studies indicate that nevirapine is widely distributed into most tissues after administration. Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. A nevirapine peak plasma concentration (C_{max}) of approximately 2 mcg/mL was measured by 4 hours after a single 200 mg dose. Following IV administration of nevirapine in healthy adults, the apparent volume of distribution is 1.21 L/kg, suggesting that the drug is widely distributed in humans. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1 to 10 mcg/ml.[8] Nevirapine concentrations in cerebrospinal fluid were 45% of the concentrations in plasma at a ratio approximately equal to the fraction not bound to plasma protein.[9] [10]

Nevirapine is extensively biotransformed via cytochrome P450 (CYP) metabolism to several hydroxylated metabolites. Biotransformation is primarily by isozymes from the CYP3A family, but other isozymes may be involved with nevirapine metabolism.[11] In a pharmacokinetic study, approximately 81% of a radiolabeled dose was recovered in the urine, with greater than 80% of that made up of glucuronide conjugates of hydroxylated metabolites. Approximately 10% of a radiolabeled dose was recovered in the feces. Less than 5% of the recovered radiolabeled dose was made up of the parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.[12] In children, nevirapine elimination accelerates during the first years of life, reaching a maximum at around 2 years of age, followed by a gradual decline during the rest of childhood.[13]

Nevirapine is in FDA Pregnancy Category B. There are no adequate and well-controlled studies of nevirapine in pregnant women. Nevirapine readily crosses the placenta and achieves neonatal blood concentrations comparable to those in the mother (cord-to-maternal blood ratio approximately 0.9). Evidence of impaired fertility was seen in female rats at doses providing systemic exposure approximately equivalent to that attained with the recommended clinical dose of nevirapine. Teratogenic effects of nevirapine have not been

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Pharmacology (cont.)

observed in reproductive studies with rats and rabbits. However, in rats, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure. Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In order to monitor maternal-fetal outcomes of pregnant women exposed to nevirapine and other antiretrovirals, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by either calling 800-258-4263 or accessing the website at <http://www.APRegistry.com>. [14] [15]

Nevirapine is readily distributed into breast milk. Following administration of a single 100- to 200-mg dose of nevirapine to pregnant women several hours prior to delivery, postpartum concentrations of nevirapine in milk have been reported to be 25% to 122% of maternal serum concentrations. HIV infected mothers should not breastfeed their infants in order to avoid risk of HIV transmission and the potential for serious nevirapine-related adverse reactions in the nursing infant. [16]

The mechanism of resistance or reduced susceptibility to nevirapine has not been fully determined, but mutation of HIV RT appears to be involved. A single mutation may be sufficient to result in high-level resistance to nevirapine. Drug-resistant HIV emerges rapidly and uniformly when nevirapine is administered as monotherapy. Mutations conferring resistance to nevirapine could be observed after a single dose, even with a low level of viral replication. Therefore, nevirapine should always be administered in combination with at least one other antiretroviral agent. [17] Resistance to nevirapine usually confers class resistance to other NNRTIs (efavirenz and delavirdine). However, nevirapine-resistant isolates were susceptible to the nucleoside analogues zidovudine and didanosine. Similarly, zidovudine-resistant isolates were susceptible to nevirapine in vitro. [18]

Nevirapine demonstrated additive to synergistic in vitro activity against HIV-1 in combination

regimens with zidovudine, didanosine, stavudine, lamivudine, saquinavir, and indinavir. [19] Because nevirapine and HIV protease inhibitors (PIs), such as amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, have different enzyme targets, cross resistance between nevirapine and these drugs is unlikely. [20]

Adverse Events/Toxicity

Granulocytopenia (occurring more frequently in children), skin rash, fever, hepatitis prodromal symptoms, hepatotoxicity, Stevens-Johnson syndrome, toxic epidermal necrolysis, gastrointestinal effects, fatigue, and headache are the most common adverse effects seen with nevirapine use. [21]

Clinically symptomatic hepatotoxicity has been observed with initiation of and during continued use of nevirapine. Among the NNRTIs, nevirapine has the greatest potential for causing clinical hepatitis. Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported in patients treated with nevirapine. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. [22] The greatest risk of severe and potentially fatal hepatic events, often associated with rash, occurs in the first 6 weeks of nevirapine treatment. Approximately two-thirds of the cases of nevirapine-associated clinical hepatitis occur within the first 12 weeks of use. [23] However, the risk continues after this time and patients should be monitored closely for the first 18 weeks of treatment. Clinical hepatitis and hepatic failure may be isolated or associated with signs of hypersensitivity, which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction. Patients who experience a clinical hepatitis event must seek medical evaluation immediately and should be advised to permanently discontinue nevirapine. In some cases, hepatic injury progresses despite discontinuation of treatment. [24] [25]

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Adverse Events/Toxicity (cont.)

Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, nevirapine should not be initiated in adult females with CD4 counts greater than 250 cells/mm³ or in adult males with CD4 counts greater than 400 cells/mm³ unless the benefit outweighs the risk.[26]

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Severe or life-threatening rash occurred in approximately 2% of clinically treated patients.[27] Fever, in the absence of any apparent cause, is a significant predictor for the development of rash in patients receiving nevirapine.[28] Patients who develop signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue nevirapine as soon as possible and must limit the nevirapine-only treatment time to 28 days.[29] [30]

The first 18 weeks of therapy with nevirapine is a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver enzyme tests at baseline, prior to dose escalation and at two weeks post-dose escalation. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash.[31]

Because most occupational HIV exposures do not result in transmission of HIV, health care providers considering prescribing postexposure prophylaxis for exposed persons must balance the risk for HIV transmission represented by the exposure and the exposure source against the potential toxicity of the

specific agents used for postexposure prophylaxis. In many circumstances, the risks associated with nevirapine as part of a postexposure prophylaxis regimen outweigh the anticipated benefits. However, no serious toxicity has been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 clinical trial regimen) for prevention of perinatal transmission of HIV.[32]

Drug and Food Interactions

Nevirapine is metabolized by and induces the activity of CYP3A isoenzymes, with maximal induction occurring within 2 to 4 weeks of initiating multidose therapy. The induction of CYP3A by nevirapine may result in lower plasma concentrations of concurrently administered drugs that are extensively metabolized by CYP3A.[33]

Caution is required when nevirapine is administered concurrently with a PI, as the plasma concentrations of PIs may be reduced to subtherapeutic concentrations due to nevirapine-induced hepatic metabolism. Nevirapine decreases the area under the plasma concentration-time curve (AUC) and C_{max} of indinavir, saquinavir, and ritonavir; nevirapine and nelfinavir do not appear to interact significantly. In contrast, PIs do not appear to affect the pharmacokinetics of nevirapine. No dosage adjustments are required when nevirapine is concurrently administered with ritonavir or nelfinavir.[34]

Concomitant use of nevirapine and hormonal contraceptives containing ethinyl estradiol or norethindrone may result in decreased plasma concentrations of the contraceptive. Therefore, hormonal contraceptives should not be used as the primary means of contraception when nevirapine is prescribed to women of childbearing potential.[35]

Concurrent use of ketoconazole with nevirapine is not recommended, as it results in significantly reduced plasma concentrations of ketoconazole and a modest increase in plasma concentrations of nevirapine. Nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concurrently.

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Drug and Food Interactions (cont.)

Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly. Concurrent use of prednisone with nevirapine has resulted in increased incidence and severity of rash in the first 6 weeks of nevirapine therapy; concurrent use is not recommended.[36]

Rifampin and rifabutin accelerate the metabolism of NNRTIs through induction of CYP isoenzymes, resulting in subtherapeutic levels of nevirapine. Nevirapine retards the metabolism of rifampin and rifabutin, resulting in increased serum levels of these drugs. A dosage adjustment may be necessary when these drugs are administered with nevirapine.[37]

Concurrent use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products with nevirapine is expected to substantially decrease nevirapine concentrations and may result in suboptimal levels of nevirapine, loss of virologic response, and development of nevirapine resistance; concurrent use is not recommended.[38]

Based on data from an open-label randomized study and retrospective database analysis demonstrating the potential for early virologic failure, clinicians are advised to use caution when co-administering tenofovir disoproxil fumarate, enteric-coated didanosine, and either efavirenz or nevirapine in the treatment of treatment-naïve HIV infected patients with high baseline viral loads.[39]

Contraindications

Nevirapine is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablet or the oral suspension.[40]

Nevirapine is contraindicated in patients with moderate or severe (child Pugh Class B or C, respectively) hepatic impairment.[41] Nevirapine is hepatotoxic and extensively metabolized by the liver. It is associated with a significant incidence of hepatotoxicity, usually occurring in the initial month of therapy. Risk-benefit should be

considered in patients with renal function impairment, as nevirapine metabolites are extensively eliminated by the kidneys.[42]

Clinical Trials

For information on clinical trials that involve Nevirapine, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Nevirapine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral (capsule, suspension).[43]

Dosage Form: Tablets containing nevirapine 200 mg.[44]

Oral suspension containing nevirapine 50 mg (as nevirapine hemihydrate) per 5 ml.[45]

The recommended adult dose of nevirapine is one 200 mg tablet once daily for the first 14 days, followed by one 200 mg tablet twice daily. As of June 2008, the recommended dose of nevirapine 50 mg/5 ml oral suspension for pediatric patients is based on body surface area (BSA) rather than on weight. Pediatric patients who are 15 days and older should receive 150 mg/m² once daily for 14 days (lead-in period) and 150mg/m² twice daily thereafter, with a maximum total daily dose of 400 mg. The decision to calculate pediatric dosing by BSA instead of weight was based on pharmacokinetic data from more than 600 participants in a 48-week pediatric trial and in an analysis of five Pediatric AIDS Clinical Trial Group protocols. BSA-calculated doses for these studies provided nevirapine trough concentrations that were comparable to those achieved with weight-based doses; however, BSA dosing was found to allow for smoother dose transitions between pediatric age groups.[46] [47] [48]

Storage: Store tablets and oral suspension at 25 C (77F), with excursions permitted between 15 C to 30 C (59 F to 86 F).[49]

Chemistry

CAS Name:

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Chemistry (cont.)

6H-Dipyrido(3,2-b:2',3'-e)(1,4)diazepin-6-one, 11-cyclopropyl-5,11-dihydro-4-methyl-[50]

CAS Number: 129618-40-2[51]

Molecular formula: C₁₅H₁₄N₄O[52]

C67.65%, H5.30%, N21.04%, O6.01%[53]

Molecular weight: 266.30[54]

Melting point: 247 to 249 C[55]

Physical Description: Tablets: White, oval, biconvex tablets with 54 193 embossed on one side.[56] Suspension: White to off-white suspension.[57]

Solubility: Solubility in water 0.1 mg/ml at neutral pH; highly soluble at pH less than 3.[58]

Other Names

BI-RG-587[59]

NVP[60]

Further Reading

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Manufacturer Information

Nevirapine
Boehringer Ingelheim Pharmaceuticals Inc
900 Ridgebury Rd / PO Box 368
Ridgefield, CT 06877-0368
(800) 542-6257

Viramune
Boehringer Ingelheim Pharmaceuticals Inc
900 Ridgebury Rd / PO Box 368
Ridgefield, CT 06877-0368
(800) 542-6257

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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