Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from http://aidsinfo.nih.gov/guidelines on 2/21/2013 EST.

Nevirapine (NVP, Viramune) (Last updated November 1, 2012; last reviewed November 1, 2012)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 200 mg, extended-release 400 mg

Suspension: 10 mg/mL

Dosing Recommendations

Neonate/infant dose (aged <14 days):

- When used for prevention of mother-to-child transmission of HIV see *Perinatal Guidelines*. Treatment dose not defined for infants aged ≤14 days.

Pediatric dose (aged ≥15 days):

See note below about initiation of therapy.

Aged <8 years:

- 200 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily

Aged ≥8 years:

- 120–150 mg/m^2 of body surface area/dose (maximum dose 200 mg) twice daily
- When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose is left static to achieve the appropriate mg/m^2 dosage as the child grows, as long as there are no untoward effects.

Note: NVP is initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P45-metabolizing enzymes, which results in increased drug clearance. The occurrence of rash is diminished by this stepwise increase in dose. Initiate therapy with the age-appropriate dose once daily for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy, increase to the age-appropriate dose administered twice daily. The total daily dose should not exceed 400 mg.

Adolescent/adult dose:

- 200 mg twice daily

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock.

Special Instructions

- Can be given without regard to food.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves (see *Major Toxicities*).
- NVP XR tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >14 days, NVP dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see text below).
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure. Patients with symptoms or signs of hepatitis should have liver function tests performed. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis or hypersensitivity reactions.

Note: Initiate therapy with 200 mg given once daily for the first 14 days. Increase to 200 mg administered twice daily if there is no rash or other untoward effects.

- 400 mg XR once daily (not approved for use in children)

Note: Initiate therapy with 200-mg immediate-release tablet given once daily for the first 14 days. Increase to 400 mg administered once daily if there is no rash or other untoward effects. In patients already receiving full-dose immediate-release NVP, extended-release tablets can be used without the 200-mg lead-in period. Patients must swallow NVP extended-release tablets whole. They must not be chewed, crushed, or divided. Patients must never take more than one form of NVP at the same time.

- *NVP in combination with lopinavir/ritonavir (LPV/r):*

A higher dose of LPV/r may be needed. See LPV/r section.

- Shake suspension well and store at room temperature

Metabolism

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites).
- Dosing of NVP in patients with renal failure receiving hemodialysis: An additional dose of NVP should be given following dialysis.
- Dosing of NVP in patients with hepatic impairment: NVP should not be administered to patients with moderate or severe hepatic impairment.

Drug Interactions (see also the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*)***:***

- *Metabolism:* Induces hepatic cytochrome P450 including 3A (CYP3A) and 2B6; auto-induction of metabolism occurs in 2 to 4 weeks, with a 1.5- to 2-fold increase in clearance. Potential exists for multiple drug interactions. Mutant alleles of CYP2B6 cause increases in nevirapine serum concentration in a similar manner but to a lesser extent than efavirenz. Altered adverse effect profiles related to elevated nevirapine levels have not been documented, probably because there are alternative CYP metabolic pathways for nevirapine.[1] Please see efavirenz section for further details.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions. Nevirapine should not be co-administered to patients receiving atazanavir (with or without ritonavir).

Major Toxicities:

Note: These are seen with continuous dosing regimens, not single-dose nevirapine prophylaxis.

- *More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated hepatic transaminases. Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. However, the risk of

developing nevirapine resistance with extended lead-in dosing is unknown and is a concern that must be weighed against a patient's overall ability to tolerate the regimen and the current antiviral response.

- *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). Most cases occur in the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for nevirapine-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 T lymphocyte (CD4 cell) count at time of therapy initiation (CD4 cell count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). In children, recent results indicate that there is a three-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with a CD4 percentage >15%.[2] Hypersensitivity reactions have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. Nevirapine should be permanently discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

Resistance: The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/NVP.html).

Pediatric Use: Nevirapine is U.S. Food and Drug Administration (FDA) approved for use in children from infancy onwards and remains a mainstay of therapy, especially in resource-limited settings. It has been studied in HIV-infected children in combination with nucleoside reverse transcriptase inhibitors (NRTIs) or with NRTIs and a protease inhibitor (PI).[3-11]

In infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission, nevirapine-based antiretroviral therapy (ART) is less likely than lopinavir/ritonavir-based ART to control virus load. In a large randomized clinical trial, P1060, 153 children (mean age 0.7 years) previously exposed to nevirapine for perinatal prophylaxis were treated with zidovudine plus lamivudine plus the randomized addition of nevirapine versus lopinavir/ritonavir. At 24 weeks post-randomization, 24% of children in the zidovudine/lamivudine/nevirapine arm reached a virologic endpoint (virologic failure defined as <1 log decrease in HIV RNA in Weeks 12–24 or HIV RNA >400 copies/mL at Week 24), compared with 7% in the zidovudine/lamivudine/lopinavir/ritonavir arm, $P = 0.0009$. When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the PI arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the lopinavir/ritonavir arm, $P = 0.027$.[12] A comparison study of nevirapine versus lopinavir/ritonavir in children aged 6 to 36 months not previously exposed to nevirapine has reported similar results, suggesting that lopinavir/ritonavir-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.[13]

Body surface area has traditionally been used to guide nevirapine dosing in infants and young children. It is important to avoid under dosing of nevirapine because a single point mutation in the HIV genome may confer non-nucleoside reverse transcriptase inhibitor resistance to both nevirapine and efavirenz. Younger children (aged ≤8 years) have higher apparent oral clearance than older children and require a higher dosage to achieve equivalent drug exposure compared with children aged >8 years.[8, 9] Because of this, it is recommended that dosing for children aged <8 years be 200 mg/m^2 of body surface area per dose (maximum dose 200 mg) administered twice daily. For children aged 8 years, the recommended dose is 120 mg/m^2 of

body surface area per dose (maximum dose 200 mg) administered twice daily. When adjusting the dose in a growing child, the milligram dosage need not be decreased (from 200 mg/m^2 to 120 mg/m^2) as the child reaches 8 years; rather, the milligram dose is left static as long as there are no untoward effects, and the dose is allowed to achieve the appropriate mg/m^2 dosage as the child grows. Some practitioners dose nevirapine at 150 mg/m^2 of body surface area every 12 hours (maximum 200 mg per dose) regardless of age, as recommended in the FDA-approved product label.

The potential for under dosing with an increased risk of resistance has led to re-evaluation of lead-in dosing in children who are naive to nevirapine therapy. Traditional dosing of nevirapine is initiated with a single daily dose during the first 2 weeks of treatment to allow for auto-induction of the liver enzymes CYP3A and CYP2B6 (which are involved in nevirapine metabolism). Studies, largely in adult cohorts, indicated the potential for greater drug toxicity without this half-dose lead-in.[14] The CHAPAS-1 Trial[15] randomized 211 children to initiate ART with either half dose or full-dose nevirapine. Children were followed for a median of 92 weeks (68–116 weeks), and there was no difference in grade 3 or 4 adverse events between the 2 groups. The full-dose nevirapine group had a statistically significant increase in grade 2 rash, but most subjects were able to continue nevirapine therapy after a brief interruption. CD4 and virologic endpoints were no different through 96 weeks. Additional trials are either in development or are under way to further evaluate the potential of initiating nevirapine therapy at full dose in treatment-naive children. Reinitiating half-dose nevirapine for another 2 weeks in children who have interrupted therapy for 7 days or longer has been standard practice; however, given the current understanding of nevirapine resistance, the half-life of the CYP enzymes,[16] and the results of CHAPAS-1, the Panel recommends restarting nevirapine at full dose in children who interrupt therapy for 14 days or less.

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in adult patients on the basis of 2 trials: VERxVE and TRANxITION. VERxVE[17] enrolled treatment-naive adults who received 200 mg of immediate-release nevirapine for 14 days before commencing daily dosing of nevirapine extended release or standard twice-daily dosing of immediate-release tablets. A backbone of tenofovir and emtricitabine was used. TRANxITION enrolled patients already receiving full-dose immediate-release nevirapine and randomized them to receive the extended-release tablets or remain on their current nevirapine regimen. VERxVE and TRANxITION have shown equivalent efficacy, adverse effect, and CD4 profiles through 48 and 24 weeks, respectively.[18] Trials are under way on use of extended-release nevirapine in patients aged <18 years.

References

1. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr*. Jul 1 2007;45(3):280-285. Available at http://www.ncbi.nlm.nih.gov/pubmed/17356468.
2. Kea C, Puthanakit T, et al. Incidence and risk factors for nevirapine related toxicities among HIV-infected Asian children randomized to starting ART at different CD4%. Abstract MOPE240. Paper presented at: 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 17-20, 2011, 2011; Rome, Italy.
3. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics*. Nov 2007;120(5):e1134-1140. Available at http://www.ncbi.nlm.nih.gov/pubmed/17954553.
4. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: Pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J*. Oct 2005;24(10):880-885. Available at http://www.ncbi.nlm.nih.gov/pubmed/16220085.

5. Krogstad P, Lee S, Johnson G, et al; Pediatric AIDS Clinical Trials Group 377 Study Team. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11880966.
6. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med*. Jun 10 2004;350(24):2471-2480. Available at http://www.ncbi.nlm.nih.gov/pubmed/15190139.
7. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. *J Infect Dis*. Oct 1996;174(4):713-721. Available at http://www.ncbi.nlm.nih.gov/pubmed/8843207.
8. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*. May 8 1997;336(19):1343-1349. Available at http://www.ncbi.nlm.nih.gov/pubmed/9134874.
9. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clinical pharmacokinetics*. Oct 2000;39(4):281-293. Available at http://www.ncbi.nlm.nih.gov/pubmed/11069214.
10. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS*. 2003;17(11):1639-1647. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12853746& query_hl=26.
11. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial-PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*. Aug 10 2000;16(12):1113-1121. Available at http://www.ncbi.nlm.nih.gov/pubmed/10954886.
12. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med*. Oct 14 2010;363(16):1510-1520. Available at http://www.ncbi.nlm.nih.gov/pubmed/20942667.
13. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med*. Jun 21 2012;366(25):2380-2389. Available at http://www.ncbi.nlm.nih.gov/pubmed/22716976.
14. Havlir D, Cheeseman SH, McLaughlin M, et al. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. *J Infect Dis*. Mar 1995;171(3):537-545. Available at http://www.ncbi.nlm.nih.gov/pubmed/7533197.
15. Mulenga V, Cook A, Walker AS, et al. Strategies for nevirapine initiation in HIV-infected children taking pediatric fixed-dose combination "baby pills" in Zambia: A randomized controlled trial. *Clin Infect Dis*. Nov 1 2010;51(9):1081-1089. Available at http://www.ncbi.nlm.nih.gov/pubmed/20868279.
16. Magnusson MO, Dahl ML, Cederberg J, Karlsson MO, Sandstrom R. Pharmacodynamics of carbamazepine-mediated induction of CYP3A4, CYP1A2, and Pgp as assessed by probe substrates midazolam, caffeine, and digoxin. *Clin Pharmacol Ther*. Jul 2008;84(1):52-62. Available at http://www.ncbi.nlm.nih.gov/pubmed/17971810.
17. Gathe J, Andrade-Villanueva J, Santiago S, et al. Efficacy and safety of nevirapine extended-release once daily versus nevirapine immediate-release twice-daily in treatment-naive HIV-1-infected patients. *Antivir Ther*. 2011;16(5):759-769. Available at http://www.ncbi.nlm.nih.gov/pubmed/21817198.
18. Boehringer Ingelheim. Virimune XR Prescribing Information. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Viramune+XR/ViramuneXR.pdf.