Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Nevirapine (NVP, Viramune) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

Formulations

Tablets: Immediate-release 200 mg, extended-release (XR) 100 mg and 400 mg
Suspension: 10 mg/mL

Generic Formulations

Tablets: Immediate-release 200 mg, extended-release (XR) 400 mg only
Suspension: Generic suspension is no longer available in the United States.

Note: While the suspension formulation of brand name nevirapine (Viramune) is available, it is not typically stocked in local pharmacies or hospitals. Have the pharmacy ask their drug wholesaler to order directly from the Boehringer-Ingleheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

Dosing Recommendations

Neonate and Infant (Aged ≤14 Days) Dose for Prevention:

- See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Table 12.

Pediatric Dose for Treatment of HIV

Note: In most situations, nevirapine is given once daily for 2 weeks to allow for autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged <2 years (see footnote[a] and text below).

Immediate Release Tablets and Suspension Formulations

*Aged <1 Month (This **Investigational Dose** is Not Food and Drug Administration-Approved):*

- 34–37 weeks gestational age: Nevirapine 4 mg/kg/dose twice daily for the first week, increasing to nevirapine 6 mg/kg/dose twice daily thereafter (no lead in; please see text and footnote[a])
- ≥37 weeks gestational age to age <1 month: Nevirapine 6 mg/kg/dose twice daily (no lead in; please see text and footnote[a])
- See the Special Considerations for Dosing: Neonates and Premature Infants section below.

Aged ≥1 Month to <8 Years:

- 200 mg/m^2 of body surface area (BSA)/dose twice daily after lead-in dosing.[a] In children aged ≤2 years, some experts initiate nevirapine without a lead-in (maximum dose of immediate-release tablets is 200 mg twice daily).

Selected Adverse Events

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

Special Instructions

- Shake suspension well before administering and store at room temperature.
- Can be given without regard to food.
- 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 (see the Major Toxicities section below).
- Nevirapine extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for more than 14 days, nevirapine should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see the Dosing Considerations: Lead-In Requirement section below).
- Most cases of nevirapine-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 (see the Major Toxicities section below).

Aged ≥8 Years:

- 120–150 mg/m^2 BSA/dose twice daily after lead-in dosing[a] (maximum dose of immediate-release tablets is nevirapine 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-per-m^2 dose as the child grows, as long as there are no untoward effects.

BSA Range	NVP XR
0.58 m^2 to 0.83 m^2	200 mg once daily (2 x 100 mg)
0.84 m^2 to 1.16 m^2	300 mg once daily (3 x 100 mg)
≥1.17 m^2	400 mg once daily (1 x 400 mg)

Key to Abbreviations: BSA = body surface area; NVP XR = nevirapine extended release

Extended-Release Formulation

Aged ≥6 Years:

- Patients aged ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine extended release without lead-in dosing.[a]

Adolescent and Adult Dose: [a,b]

- 200 mg twice daily or 400 mg extended release once daily after lead-in dosing.

Nevirapine Used in Combination with Lopinavir/Ritonavir:

- A higher dose of lopinavir/ritonavir may be needed (see Lopinavir/Ritonavir).
- Nevirapine **should not be co-administered** to patients receiving atazanavir (with or without ritonavir).
- Nevirapine increases the metabolism of lopinavir. A dose adjustment of lopinavir is recommended (see Lopinavir/Ritonavir).

Metabolism/Elimination

- Metabolized by cytochrome P450 (3A inducer); 80% of nevirapine dose is excreted in urine (glucuronidated metabolites).

Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis:

- An additional dose of nevirapine should be given following dialysis.

Nevirapine Dosing in Patients with Hepatic Impairment:

- Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

[a] Nevirapine is usually initiated at a lower dose and increased in a stepwise fashion to allow for induction of cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians should initiate therapy with the age-appropriate dose of the immediate-release formulation once daily (half-daily dose) 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 full dose, administered twice daily, of the immediate-release preparation. However, in children aged ≤2 years, some experts initiate nevirapine without a lead-in (see Dosing Considerations: Lead-In Requirement and Special Considerations for Dosing: Neonates and Premature Infants sections below). In patients who are already receiving full-dose, immediate-release nevirapine, extended-release tablets can be used without the 200-mg lead-in period. Patients must swallow nevirapine extended-release tablets whole. They must not be chewed, crushed, or divided. Patients must **never** take more than 1 form of nevirapine at the same time. Dose should not exceed 400 mg daily.

[b] Symptomatic hepatitis, including fatal hepatic necrosis, occurs at a significantly higher frequency in antiretroviral (ARV)-naive women with pre-nevirapine CD4 T lymphocyte (CD4) cell counts >250 cells/mm^3 and in ARV-naive men with pre-nevirapine CD4 counts >400 cells/mm^3. Nevirapine **should not be initiated** in these patients unless the benefit clearly outweighs the risk.

Drug Interactions (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- *Metabolism:* Induces hepatic cytochrome P450, including 3A (CYP3A) and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, with a 1.5- to two-fold increase in nevirapine clearance. There is potential for multiple drug interactions. Some genetic polymorphisms of CYP2B6 can increase in nevirapine serum concentration by affecting drug metabolism in a similar manner—but to a lesser extent—than the changes observed with 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] however, CYP2B6 polymorphisms can vary greatly among populations, which may account for differences in drug exposure. Please see Efavirenz section for further details.

- Before nevirapine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

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

- *More common:* Skin rash (some severe cases have required hospitalization, and some cases have been life-threatening, including instances of Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be 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 the 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 the current antiviral response and a patient's overall ability to tolerate the regimen.
- *Less common (more severe):* Severe, life-threatening, and, in rare cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these toxicities are less common in children than adults). The majority of 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 hepatitis C virus 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, 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 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 and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

Nevirapine is Food and Drug Administration (FDA)-approved for treatment of HIV in children from infancy (aged ≥15 days) onward and remains a mainstay of therapy, especially in resource-limited settings.[3-11] The extended-release tablet formulation has been FDA-approved for use in children aged ≥6 years.

Efficacy in Clinical Trials

Randomized clinical trials in children have demonstrated that lopinavir/ritonavir (LPV/r) is superior to nevirapine in young children but not in older children. P1060 demonstrated the superiority of LPV/r over nevirapine in children aged <3 years, as have observational studies. PENPACT-1 and PROMOTE-pediatrics enrolled older children receiving nevirapine or efavirenz and showed no differences between a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and protease inhibitor (PI)-based regimen.[12-18]

In infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission,

nevirapine-based antiretroviral therapy (ART) is less likely to control viral load than LPV/r-based ART. In P1060, a large randomized clinical trial, 153 children with HIV and previous exposure to nevirapine for perinatal prophylaxis (mean age 0.7 years) were randomly assigned to treatment with zidovudine and lamivudine plus either nevirapine or LPV/r. 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 to 24 or HIV RNA >400 copies/mL at Week 24) compared with 7% of children 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% of children in the LPV/r arm ($P = 0.027$).[15] Similar results were reported in a comparison study of nevirapine and LPV/r in children aged 6 to 36 months **not** previously exposed to nevirapine, suggesting that LPV/r-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.[12]

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in children aged ≥6 years in November 2012. Trial 1100.1518 was an open-label, multiple-dose, nonrandomized, crossover trial performed in 85 pediatric participants with HIV. The participants had received at least 18 weeks of immediate-release nevirapine and had plasma HIV RNA <50 copies per mL prior to enrollment. Participants were stratified according to age (aged 3 years to <6 years, 6 years to <12 years, and 12 years to <18 years). Following an 11-week period with immediate-release nevirapine, participants were treated with nevirapine extended-release tablets once daily in combination with other antiretroviral (ARV) drugs for 10 days, after which steady-state pharmacokinetics (PK) were determined.[19] Forty participants who completed the initial part of the study were enrolled in an optional extension phase of the trial, which evaluated the safety and antiviral activity of nevirapine extended release through a minimum of 24 weeks of treatment. Of the 40 participants who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with nevirapine extended release, all 39 participants continued to have plasma HIV RNA <50 copies per mL.[20]

General Dosing Considerations

Body surface area (BSA) 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 (K103N) in the HIV genome may confer NNRTI resistance to both nevirapine and efavirenz. Younger children (aged ≤8 years) have higher apparent oral clearance than older children. In order to achieve drug exposures that are equivalent to those seen in children aged >8 years, younger children require higher doses of nevirapine than older children.[8,9] Because of this, it is recommended that dosing for children aged <8 years be nevirapine 200 mg/m^2 of BSA per dose when given twice daily (maximum dose of the immediate-release preparation is 200 mg twice daily) or nevirapine 400 mg/m^2 of BSA per dose when administered once daily as the extended-release preparation (maximum dose of the extended-release preparation is nevirapine 400 mg/dose once daily). For children aged ≥8 years, the recommended dose of the immediate-release preparation is nevirapine 120 mg/m^2 of BSA per dose (with a maximum dose of nevirapine 200 mg) administered twice daily. The maximum dose of the extended-release preparation is nevirapine 400 mg once daily for children aged ≥6 years. When adjusting the dose in a growing child, the milligram dose need not be decreased (from nevirapine 200 mg/m^2 to 120 mg/m^2) as the child reaches 8 years; rather, the milligram dose is left static if there are no untoward effects, and the dose is allowed to achieve the appropriate mg/m^2 dose as the child grows. Some practitioners dose nevirapine at 150 mg/m^2 of BSA every 12 hours or nevirapine 300 mg/m^2 per dose once daily if using the extended-release preparation (with a maximum of nevirapine 200 mg per dose twice daily for the immediate-release tablets or nevirapine 400 mg per dose once daily for the extended-release tablets) regardless of age, as recommended in the FDA-approved product label.

Dosing Considerations: Lead-In Requirement

One explanation for the poorer performance of nevirapine in the P1060 trial was the potential for under-dosing during the lead-in period. This 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 an age-appropriate dose once daily (nevirapine 200 mg/m^2 in infants aged ≥15 days and children aged <8 years using the immediate-release preparations) during the first 2 weeks of treatment to allow for the autoinduction of the liver enzymes CYP3A and CYP2B6, which are involved in nevirapine metabolism.

Studies have previously indicated that there is a potential for greater drug toxicity without lead-in dosing; however, most of these studies have been performed in adult cohorts.[21] The CHAPAS-1 Trial[22] randomized 211 children to initiate ART with immediate-release nevirapine without a lead-in (age-appropriate dose given twice daily) or with a lead-in (age-appropriate dose given once daily) for 2 weeks followed by standard twice-daily dosing of the immediate-release preparation. Children were followed for a median of 92 weeks (with a range of 68–116 weeks), and there was no difference in the frequency of Grade 3 or 4 adverse events between the two groups. The group that initiated nevirapine without a lead-in had a statistically significant increase in Grade 2 rash, but the majority of subjects were able to continue nevirapine therapy after a brief interruption. CD4 and virologic endpoints were no different through 96 weeks. After children had been on nevirapine for two weeks, investigators conducted a substudy that examined nevirapine plasma concentrations 3 to 4 hours after a morning dose of nevirapine.

For children aged <2 years, 13% (3/23) initiating at full dose versus 32% (7/22) initiating at half dose had subtherapeutic nevirapine levels (<3 mg/L) at 2 weeks (P = 0.16). There were no rash events in the substudy group of participants aged <2 years; in the parent CHAPAS study, there was a strong age effect on rash occurrence, with the risk of rash increasing with increasing age). These findings suggest that a lead-in dose may not be necessary in young patients.[23]

A re-appraisal of nevirapine dosing has been advocated in older children. Gopalan et al. analyzed nevirapine concentrations in 20 children, median age 9 years, who were just starting a nevirapine-based ART regimen. Subtherapeutic nevirapine concentrations, which were defined as concentrations ≤4 mcg/mL, occurred more frequently among children aged ≤8 years (n = 8) than among children aged >8 years (n = 12). Half of the children experienced virologic failure by Week 48.[24] Gopalan et al. suggested that rapid metabolism of nevirapine by CYP2B6 in this particular population may have confounded the results. The small number of participants in this study make the findings difficult to interpret, but the authors recommended a thorough review of nevirapine dose escalation strategies in 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,[25] and the results of CHAPAS-1, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends restarting full-dose nevirapine in children who interrupt therapy for 14 days or less.

Special Considerations for Dosing: Neonates and Premature Infants

For neonates and premature infants (which includes infants up to 42 weeks, corrected gestational age), PK data are currently inadequate to formulate an effective complete ART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of ART. On the basis of PK modeling, an investigational dose of nevirapine 6 mg/kg administered twice daily has been proposed for full-term infants who receive HIV diagnoses in the first few days of life.[26-30] However, a dose of nevirapine 4 mg/kg/dose twice daily has been chosen for the first week of life in infants born between 34 and 37 weeks' gestation, followed by a nevirapine 6 mg/kg/dose administered twice daily thereafter. Dose adjustments may be required if a premature infant has documented HIV infection in the first week of life. PK of nevirapine using the investigational dose will be evaluated as part of IMPAACT 1115. Initial results from this study indicate that the experimental dosing schedule is safe and provides adequate PK to maintain trough concentrations of nevirapine greater than 3 mcg/mL in the majority of infants.[31] Providers considering treatment of infants aged <2 weeks or premature infants should contact a pediatric HIV expert for guidance, because the decision about whether to treat an infant and what drugs to use will involve weighing the risks and benefits of using unapproved ART dosing and incorporating case-specific factors, such as exposure to ARV prophylaxis.

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