Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Nevirapine (NVP, Viramune) (Last updated April 16, 2019; last reviewed April 16, 2019)

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:
- Immediate-release 200 mg tablets
- Extended-release (XR) 400 mg tablets

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 from the Boehringer-Ingelheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

Dosing Recommendations

Note: Nevirapine is often used to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV for information about nevirapine dosing in neonates aged ≤ 1 days.

Child and Adolescent Dose:
- 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.

Immediate-Release Tablets and Suspension Formulations

Gestational Age 34 Weeks–37 Weeks:
- Nevirapine 4 mg/kg per dose twice daily for the first week, increasing to nevirapine 6 mg/kg per dose twice daily thereafter (no lead-in dosing).
- This is an investigational dose that is not approved by the Food and Drug Administration (FDA).

Gestational Age ≥37 Weeks to Age <1 Month:
- Nevirapine 6 mg/kg per dose twice daily (no lead-in dosing).
- This is an investigational dose that is not approved by the FDA.
- See the Special Considerations for Dosing: Neonates and Premature Infants section below.

Aged ≥1 Month to <8 Years:
- Nevirapine 200 mg/m² of body surface area per dose twice daily after lead-in dosing. In children aged ≤ 2 years, some experts initiate

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

- Shake suspension well before administering and store at room temperature.
- Nevirapine 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 Major Toxicities below).
- Nevirapine extended-release tablets must be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for >14 days, nevirapine should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see Dosing Considerations: Lead-In Requirement 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 Major Toxicities below).
Nevirapine is usually initiated at a lower dose that is increased in a stepwise fashion. Nevirapine induces CYP metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians should initiate therapy with the immediate-release formulation once daily instead of twice daily for the first 14 days of therapy. If there are no rash or other adverse effects after 14 days of therapy, increase the dose of nevirapine to the age-appropriate full dose of the immediate-release formulation administered twice daily. For example, the recommended oral dose for pediatric patients aged ≥1 month to <8 years is nevirapine 200 mg per m² of body surface area once daily for the first 14 days, followed by nevirapine 200 mg per m² of body surface area twice daily thereafter. However, in children aged ≤2 years, some experts initiate nevirapine without lead-in dosing (see Dosing Considerations: Lead-In Requirement and Special Considerations for Dosing: Neonates and Premature Infants below). In patients who are already receiving the full twice-daily dose of immediate-release nevirapine, extended-release tablets can be used without the 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 one form of nevirapine at the same time. The dose should not exceed 400 mg daily.

### Metabolism/Elimination
- Nevirapine is a substrate and inducer of cytochrome P450 (CYP) 3A4 and CYP2B6. More than 80% of a nevirapine dose is eliminated in urine as UGT-derived glucuronidated metabolites.

### Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis:
- An additional dose of nevirapine should be given following each dialysis session.

### Nevirapine Dosing in Patients with Hepatic Impairment:
- Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

### Extended-Release Tablets

#### 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.

<table>
<thead>
<tr>
<th>Body Surface Area Range</th>
<th>Nevirapine Extended-Release Tablets</th>
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<tbody>
<tr>
<td>0.58 m² to 0.83 m²</td>
<td>200 mg once daily (two 100-mg tablets)</td>
</tr>
<tr>
<td>0.84 m² to 1.16 m²</td>
<td>300 mg once daily (three 100-mg tablets)</td>
</tr>
<tr>
<td>≥1.17 m²</td>
<td>400 mg once daily (one 400-mg tablet)</td>
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### Body Surface Area Dosing for Nevirapine Extended-Release Tablets

#### Adolescent and Adult Dose:
- Nevirapine 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 the Lopinavir/ritonavir section).

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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/mm² and in ARV-naive men with pre-nevirapine CD4 counts >400 cells/mm². Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk.
Drugs Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Nevirapine induces hepatic cytochrome P450 (CYP), including 3A and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, leading to a 1.5- to two-fold increase in nevirapine clearance. There is potential for multiple drug interactions with nevirapine. Some genetic polymorphisms of CYP2B6 are associated with increased nevirapine serum concentrations. CYP2B6 polymorphisms vary among populations and may contribute to differences in nevirapine exposure. Please see the Efavirenz section for more information on how polymorphisms can alter enzyme activity.

- Nevirapine should not be coadministered to patients who are receiving atazanavir (with or without ritonavir), because nevirapine substantially decreases atazanavir exposure.

- Nevirapine increases the metabolism of lopinavir. A dose adjustment of lopinavir is recommended when the two drugs are coadministered (see the Lopinavir/ritonavir section).

- 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 levels of 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 this concern 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 during 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 sex, and higher CD4 T lymphocyte (CD4) cell count at time of therapy initiation (CD4 cell count >250 cells/mm³ in adult females and >400 cells/mm³ in adult males). In children, there is a three-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with CD4 percentages >15%. 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 Antiviral 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 approved by the Food and Drug Administration (FDA) for treatment of HIV in children from infancy (aged ≥15 days) onward and remains a mainstay of therapy, especially in resource-limited settings.
The extended-release tablet formulation has been approved by the FDA 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. IMPAACT 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.11-17

In infants and children who were previously exposed to a single dose of nevirapine to prevent perinatal transmission of HIV, nevirapine-based antiretroviral therapy (ART) is less likely to control viral load than LPV/r-based ART. In P1060, 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 nevirapine arm had experienced virologic failure, defined as <1 log₁₀ decrease in HIV RNA during Weeks 12 to 24 or HIV RNA >400 copies/mL at Week 24, compared to 7% of children in the LPV/r arm (P = 0.0009). When all primary endpoints were considered, including virologic failure, death, and treatment discontinuation, the PI arm remained superior; 40% of children in the nevirapine arm met a primary endpoint compared to 22% of children in the LPV/r arm (P = 0.027).14 Similar results were reported in a comparison study of nevirapine and LPV/r in children aged 6 to 36 months who had not been previously exposed to nevirapine. This finding suggests that LPV/r-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.11

Extended-release nevirapine tablets (400 mg) were 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/mL prior to enrollment. Participants were stratified according to age (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 (PKs) were determined.18 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/mL.19

**General Dosing Considerations**

Body surface area has traditionally been used to guide nevirapine dosing in infants and young children. It is important to avoid underdosing nevirapine, because a single point mutation (K103N) in the HIV genome may confer NNRTI resistance to both nevirapine and efavirenz. Younger children (those 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.78 Because of this, it is recommended that children aged <8 years receive nevirapine 200 mg per m² of body surface area per dose twice daily (the maximum dose of the immediate-release preparation is 200 mg twice daily) or nevirapine 400 mg per m² of body surface area administered once daily as the extended-release preparation (the maximum dose of the extended-release preparation is nevirapine 400 mg once daily). For children aged ≥8 years, the recommended dose of the immediate-release preparation is nevirapine 120 mg per m² of body surface area 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 for a growing child, the milligram dose need not be decreased (from nevirapine 200 mg to 120 mg per m² of body surface area) as the child reaches 8 years of age; rather, the
milligram dose is left static if there are no adverse effects, and the dose is allowed to achieve the appropriate mg per m² of body surface area dose as the child grows. Some practitioners dose nevirapine at 150 mg per m² of body surface area every 12 hours or nevirapine 300 mg per m² of body surface area 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 once daily for the extended-release tablets) regardless of age, as recommended in the FDA-approved product label.

Dosing Considerations: Lead-In Requirement

Underdosing during the lead-in period may have potentially contributed to the poorer performance of nevirapine in the P1060 trial. This potential for underdosing, which can increase the risk of resistance, has led to re-evaluation of lead-in dosing in children who are naive to nevirapine therapy. Traditionally, nevirapine is initiated with an age-appropriate dose that is given only once daily instead of twice daily (nevirapine 200 mg per m² of body surface area 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.20 The CHAPAS-1 trial21 randomized 211 children to initiate ART with immediate-release nevirapine without a lead-in dose (participants received an age-appropriate dose twice daily) or with a lead-in dose (participants received an age-appropriate dose 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 dose had a statistically significant increase in the incidence of Grade 2 rash, but the majority of participants were able to continue nevirapine therapy after a brief interruption. Through 96 weeks, a similar percentage of participants in both groups reached the CD4 cell count and virologic failure endpoints.

After children had been on nevirapine for 2 weeks, investigators conducted a substudy that examined nevirapine plasma concentrations 3 to 4 hours after a morning dose of nevirapine. Among children aged <2 years, three of 23 children (13%) who initiated at full dose had subtherapeutic nevirapine levels (<3 mg/L) at 2 weeks compared to seven of 22 children (32%) who initiated at half dose (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.22

Gopalan et al. analyzed nevirapine concentrations in 20 children who had a median age of 9 years and who were just starting a nevirapine-based ART regimen. Subtherapeutic nevirapine concentrations, which were defined as trough 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 aged ≤8 years experienced virologic failure by Week 48.23 The authors of the study 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,24 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 with corrected gestational ages of up to 42 weeks), PK data are currently inadequate to formulate an effective ART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for determining the appropriate doses for other ARV drugs. 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. However, a dose of nevirapine 4 mg/kg per 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 per dose administered twice daily thereafter. Dose adjustments may be required if a premature infant is found to have HIV during the first week of life. The PKs of nevirapine in patients who receive 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 PKs to maintain trough concentrations of nevirapine >3 mcg/mL in the majority of infants. Providers who are considering initiating treatment in infants aged <2 weeks or in 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.

References


