



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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## Nevirapine (NVP, Viramune) (Last updated April 27, 2017; last reviewed April 27, 2017)

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:** No longer available in the United States

### Dosing Recommendations

#### Neonate/Infant Dose ( $\leq 14$ Days) for Prevention:

- See [Infant Antiretroviral Prophylaxis and Neonatal Antiretroviral Drug Dosing](#) of the [Perinatal Guidelines](#) for dosing.

#### Treatment of HIV Infection:

*Pediatric Dose: Immediate Release and Suspension Formulations*

- In most situations, nevirapine is given once daily for 2 weeks to allow for autoinduction of enzymes involved in its metabolism. This may not be necessary in children aged  $< 2$  years. See text and footnote.<sup>a</sup>

*Aged  $< 1$  Month (Investigational dose not Food and Drug Administration approved):*

- 34–37 weeks gestational age (no lead in; please see text and footnote<sup>a</sup>): 4 mg/kg/dose twice daily for the first week increasing to 6 mg/kg/dose twice daily thereafter
- $\geq 37$  weeks gestational age to  $< 1$  month: 6 mg/kg/dose twice daily (no lead in; please see text and footnote<sup>a</sup>)
- See [Dosing: Special Considerations: Neonates  \$\leq 14\$  Days and Premature Infants](#)

*Aged  $\geq 1$  Month to  $< 8$  Years:*

- 200 mg/m<sup>2</sup> of body surface area (BSA)/dose twice daily after lead-in dosing.<sup>a</sup> In children aged  $\leq 2$  years, some experts initiate nevirapine without a lead-in (maximum dose of immediate-release tablets is 200 mg twice daily).

*Aged  $\geq 8$  Years:*

- 120–150 mg/m<sup>2</sup> BSA/dose twice daily after lead-in dosing<sup>a</sup> (maximum dose of immediate-release tablets is 200 mg twice daily.)
- When adjusting the dose for a growing child,

### 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.
- 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](#) section).
- 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 dosing 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](#)).
- 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](#)).

### Metabolism/Elimination

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine

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<sup>2</sup> dosage as the child grows, as long as there are no untoward effects.

BSA Range (m <sup>2</sup> )	NVP XR (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)

**Key to Abbreviations:** BSA = body surface area; NVPXR = nevirapine extended release

### Pediatric Dose Extended-Release Formulation (≥6 Years):

- Patients ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine extended release without lead-in dosing. **Please see footnote.<sup>a</sup>**

### Adolescent and Adult Dose:

- 200 mg twice daily or 400 mg extended release once daily.

### Nevirapine in Combination with Lopinavir/Ritonavir:

A higher dose of ritonavir-boosted lopinavir may be needed (see [Ritonavir-Boosted Lopinavir](#) section).

(glucuronidated metabolites).

- Dosing of nevirapine in patients with renal failure receiving hemodialysis:** An additional dose of nevirapine should be given following dialysis.
- Dosing of nevirapine in patients with hepatic impairment:** Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

<sup>a</sup> Nevirapine is **usually** initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P450 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 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 [Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants](#)). In patients 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.

**Drug Interactions** (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#) and <http://www.hiv-druginteractions.org/>)

- 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. There is potential 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<sup>1</sup>; however, CYP2B6 polymorphisms can vary greatly among populations, which may account for differences in drug exposure. 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). Nevirapine increases the metabolism of lopinavir and dosage adjustment is**

**recommended** (see [Lopinavir/Ritonavir](#) section).

## 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). 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<sup>3</sup> in adult females and >400 cells/mm<sup>3</sup> in adult males). In children, there is a 3-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with a CD4 percentage >15%.<sup>2</sup> 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://iasusa.org/sites/default/files/tam/october\\_november\\_2015.pdf#page=10](http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/DR>).

## 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.<sup>3-11</sup> 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 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 an NNRTI-based and PI-based regimen.<sup>12-18</sup>

In infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission; nevirapine-based antiretroviral therapy (ART) is less likely than LPV/r-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 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 12–24 or HIV RNA >400 copies/mL at Week 24) compared with 7% in the zidovudine/lamivudine/LPV/r arm,  $P = 0.0009$ . When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the protease inhibitor (PI) arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the LPV/r arm,  $P = 0.027$ .<sup>15</sup> Similar results were reported in a comparison study of nevirapine versus LPV/r in children aged 6 to 36 months **not** previously exposed to nevirapine, suggesting that lopinavir/ritonavir-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.<sup>12</sup>

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in children aged  $\geq 6$  years in November 2012. Trial 1100.1518 was an open-label, multiple-dose, non-randomized, crossover trial performed in 85 pediatric participants with HIV aged 3 years to <18 years who had received at least 18 weeks of immediate-release nevirapine and had plasma HIV-1 RNA <50 copies per mL prior to trial enrollment. Participants were stratified according to age (3 to <6 years, 6 to <12 years, and 12 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.<sup>19</sup> 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-1 RNA <50 copies per mL.<sup>20</sup>

### ***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 non-nucleoside reverse transcriptase inhibitor resistance to both nevirapine and efavirenz. Younger children ( $\leq 8$  years of age) have higher apparent oral clearance than older children and require a higher dosage to achieve equivalent drug exposure compared with children aged >8 years.<sup>8,9</sup> Because of this, it is recommended that dosing for children aged <8 years be 200 mg/m<sup>2</sup> of BSA per dose when given twice daily (immediate-release tablet maximum dose 200 mg twice daily) or 400 mg/m<sup>2</sup> of BSA per dose when administered once daily as the extended-release preparation (maximum dose of the extended-release preparation 400 mg/dose once daily). For children aged  $\geq 8$  years, the recommended dose is 120 mg/m<sup>2</sup> of BSA per dose (maximum dose 200 mg) administered twice daily to a maximum of 400 mg once daily when the extended-release preparation is used in children aged  $\geq 6$  years. When adjusting the dose in a growing child, the milligram dose need not be decreased (from 200 mg/m<sup>2</sup> to 120 mg/m<sup>2</sup>) 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<sup>2</sup> dosage as the child grows. Some practitioners dose nevirapine at 150 mg/m<sup>2</sup> of BSA every 12 hours or 300 mg/m<sup>2</sup> per dose once daily if using the extended-release preparation (maximum of 200 mg per dose twice daily of the immediate-release tablets or 400 mg per dose once daily of 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 (200 mg/m<sup>2</sup> in infants  $\geq 15$  days and children <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, largely in adult cohorts, previously indicated the potential for greater drug toxicity without this lead-in.<sup>21</sup> The CHAPAS-1 Trial<sup>22</sup> randomized 211 children to initiate ART with nevirapine without a lead-in (age-appropriate dose, twice daily, of the immediate-release preparation) or with a lead-in (age-appropriate dose, once daily, of the immediate-release preparation) for 2 weeks followed by standard twice-daily dosing of



the immediate-release preparation. Children were followed for a median of 92 weeks (68–116), and there was no difference in grade 3 or 4 adverse events between the 2 groups. The group initiating 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. In a substudy of this trial, the investigators evaluated nevirapine plasma concentrations 3 to 4 hours after a morning dose of nevirapine after 2 weeks of therapy. For children aged <2 years, 13% (3/23) initiating at full dose versus 32% (7/22) initiating at half dose had sub-therapeutic nevirapine levels (<3 mg/L) at 2 weeks ( $P = 0.16$ ). There were no rash events in the substudy group aged <2 years and in the parent CHAPAS study there was a strong age effect on rash occurrence (increased risk with increasing age), suggesting that a lead-in dose may not be necessary in young patients.<sup>23</sup> 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,<sup>24</sup> and the results of CHAPAS-1, the Panel recommends restarting full-dose nevirapine in children who interrupt therapy for 14 days or less.

### ***Dosing: Special Considerations: Neonates and Premature Infants***

For neonates and for premature infants (until 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. Based on PK modeling, an investigational nevirapine dose of 6 mg/kg administered twice daily has been proposed for full-term infants diagnosed as infected in the first few days of life.<sup>25–28</sup> However, a dose of 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 6 mg/kg/dose 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 the majority of infants with trough concentrations of nevirapine greater than 3 mcg/mL.**<sup>29</sup> Providers considering treatment of infants <2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what 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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