Nelfinavir (NFV, Viracept)

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<table>
<tr><th colspan="2">Formulations</th></tr>
<tr><td colspan="2">Tablets: 250 mg and 625 mg

For additional information, see Drugs@FDA.</td></tr>
<tr><th>Dosing Recommendations</th><th>Selected Adverse Events</th></tr>
<tr><td rowspan="4">Note: The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV no longer recommends nelfinavir-based regimens for use in children due to inferior potency compared to other regimens.

Neonate and Infant Dose

• Nelfinavir should not be used for treatment in children aged <2 years.

Pediatric Dose (Aged ≥2 Years)

• 45–55 mg/kg twice daily

Adolescent and Adult Dose

• 1,250 mg (five 250-mg tablets or two 625-mg tablets) twice daily</td><td>• Diarrhea
• Hyperlipidemia
• Hyperglycemia
• Fat maldistribution
• Serum transaminase elevations</td></tr>
<tr><th>Special Instructions</th></tr>
<tr><td>• Administer nelfinavir with meal or light snack.
• If co-administered with didanosine, administer nelfinavir 2 hours before or 1 hour after didanosine.
• Patients unable to swallow nelfinavir tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding or other nonacidic foods.</td></tr>
<tr><th>Metabolism/Elimination</th></tr>
<tr><td>• Cytochrome P (CYP) 2C19 and 3A4 substrate
• Metabolized to active M8 metabolite
• CYP3A4 inhibitor</td></tr>
</table>

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Cytochrome P (CYP) 2C19 and 3A4 substrate and CYP3A4 inhibitor. Ritonavir boosting does not significantly increase nelfinavir concentrations, and co-administration of nelfinavir with ritonavir **is not recommended**.
- There is potential for multiple drug interactions with nelfinavir. Before administering nelfinavir, carefully review a patient's medication profile for potential drug interactions.

Major Toxicities

- *More common:* Diarrhea (most common), asthenia, abdominal pain, rash, lipid abnormalities
- *Less common (more severe):* Fat redistribution, exacerbation of chronic liver disease
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in patients with hemophilia, elevations in transaminases

Resistance

The International AIDS Society–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

Nelfinavir is approved by the Food and Drug Administration (FDA) for use in children aged ≥2 years. Given the higher variability of nelfinavir plasma concentrations in infants and younger children,[1,2] nelfinavir is not approved for children aged <2 years. Despite being FDA-approved for pediatric use, nelfinavir **is not recommended** for use in children and adolescents by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, due to its limited efficacy and uncertain pharmacokinetics (PK).

Efficacy in Pediatric Clinical Trials

Nelfinavir used in combination with other antiretroviral (ARV) drugs has been extensively studied in children with HIV infection.[3-10] In randomized trials of children aged 2 to 13 years receiving nelfinavir as part of triple combination therapy, the proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. The antiviral response to nelfinavir is significantly less in children aged <2 years than in older children.[8,10,11] In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient's age or prior treatment history, the number of drugs included in the combination regimen, and the dose of nelfinavir used.

Pharmacokinetics: Exposure-Response Relationships

Nelfinavir's relatively poor ability to control plasma viremia in infants and children in clinical trials may be related to its lower potency when compared with other ARV drugs, as well as highly variable drug exposure, metabolism, and poor palatability.[12-14] The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.[3,15]

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve increases by up to fivefold) and decreases PK variability when compared to the fasted state. Nelfinavir plasma exposure may be even more unpredictable in pediatric patients than in adults due to the increased clearance of nelfinavir observed in children and difficulties in taking nelfinavir with sufficient food to improve bioavailability.

Nelfinavir is metabolized by multiple CYP450 enzymes, including CYP3A4 and CYP2C19. The variability of drug exposure at any given dose is much higher for children than for adults,[16] which has been attributed—at least in part—to differences in the diets of children and adults. Two population PK studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability

observed in children.[17,18] Furthermore, CYP2C19 genotype has been shown to affect nelfinavir PK and the virologic responses in children with HIV.[12]

Several studies have demonstrated a correlation between nelfinavir trough concentrations and virologic response. In both children and adults, an increased risk of virologic failure was associated with low nelfinavir drug exposure, particularly with a nelfinavir minimum plasma concentration (C_{min}) <1.0 mcg/mL.[19-21]

In a study of 32 children treated with a high dose of nelfinavir (a twofold increase of the recommended dose), 80% of children with morning trough nelfinavir plasma concentration >0.8 mcg/mL had HIV RNA concentrations <50 copies/mL at Week 48, compared with only 29% of those with morning trough <0.8 mcg/mL.[22] Children in the group with C_{trough} <0.8 mcg/mL were younger than the children in the group with C_{trough} >0.8 mcg/mL (median ages in these groups were 3.8 years and 8.3 years, respectively).[22] Therapeutic drug monitoring of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, has been shown to improve virologic response in adults and children.[18,19,23,24] Pediatric and adolescent and patients may require doses higher than those recommended in adults to achieve higher plasma nelfinavir exposure.

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