



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Ritonavir (RTV, Norvir) (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

Oral solution (contains 43% alcohol by volume): 80 mg/mL

Capsules: 100 mg

Tablets: 100 mg

Dosing Recommendations

RTV as a pharmacokinetic (PK) enhancer:

The major use of RTV is as a PK enhancer of other protease inhibitors used in pediatric patients and in adolescents and adults. The dose of RTV recommended varies and is specific to the drug combination selected. See dosing information for specific protease inhibitors (PIs).

In the unusual situation when RTV is prescribed as sole PI:

- See manufacturer guidelines.

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Paresthesias (circumoral and extremities)
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

Special Instructions

- Administer RTV with food to increase absorption and reduce GI side effects.
- If RTV is prescribed with didanosine (ddI), administer the drugs 2 hours apart.
- Refrigerate RTV capsules only if the capsules will not be used within 30 days or cannot be stored below 77°F (25°C). RTV tablets are heat stable.
- Do not refrigerate RTV oral solution; store at room temperature (68–77°F or 20–25°C). Shake the solution well before use.
- RTV oral solution has limited shelf life; use within 6 months.
- Patients who have persistent or significant nausea with the capsule may benefit from switching to the tablet. Also, the tablet is smaller than the capsule and thus easier to swallow.

To increase tolerability of RTV oral solution in children:

- Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
- Before administration, give a child ice chips, a popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds, or give peanut butter to coat the mouth.
- After administration, give a child strong-tasting foods such as maple syrup, cheese, or highly flavored chewing gum.

Metabolism

- Cytochrome P (CYP)3A4 and CYP 2D6 inhibitor; CYP3A4 and CYP1A2 inducer.

Dosing of RTV in patients with hepatic impairment:

- RTV is primarily metabolized by the liver. No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. Data are unavailable on RTV dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering RTV to patients with moderate-to-severe hepatic impairment.

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

- *Metabolism:* Ritonavir is extensively metabolized by and is one of the most potent inhibitors of hepatic cytochrome P450 3A (CYP3A). There is potential for multiple drug interactions with ritonavir.
- Before ritonavir is administered, a patient's medication profile should be carefully reviewed for potential interactions with ritonavir and overlapping toxicities with other drugs.
- Avoid concomitant use of intranasal or inhaled fluticasone. Use caution when prescribing ritonavir with other inhaled steroids because of reports of adrenal insufficiency.¹⁻³

Major Toxicities:

- *More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesia, lipid abnormalities.
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema.

Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.⁴

Resistance: Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other protease inhibitors (PIs).

Pediatric Use: Ritonavir has been approved by the Food and Drug Administration (FDA) for use in the pediatric population. Use of ritonavir as the sole PI in antiretroviral therapy (ART) in children is not recommended. However, in both children and adults, ritonavir is recommended as a PK enhancer to boost another/second PI in an ART regimen. Ritonavir acts by inhibiting the metabolism of the second (boosted) PI in the regimen, thereby increasing the plasma concentration of the second/boosted PI. Lopinavir/ritonavir, a PI coformulation, has been well studied in children and is a preferred PI for therapy in children (see [Lopinavir/Ritonavir](#)). Pediatric dosing regimens including boosted fosamprenavir, tipranavir, darunavir, and atazanavir are available (see individual PIs for more specific information).

Although ritonavir has been well studied, its use in children as a sole PI for therapy is limited because ritonavir is associated with a higher incidence of GI toxicity and has a greater potential for drug-drug interactions than other PIs. Also, ritonavir as a sole PI is associated with a higher risk of virologic failure than efavirenz or lopinavir/ritonavir.⁵⁻⁷ In addition, poor palatability of the liquid preparation and large pill burden with the capsules (adult dose is six capsules or tablets twice daily) limit its use as a sole PI. Concentrations are highly variable in children younger than 2 years, and doses of 350 to 450 mg/m² twice a day may not be sufficient for long-term suppression of viral replication in this age group.⁸⁻¹⁹

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir at 400 mg twice daily.⁴ Potentially life-threatening arrhythmias in premature newborn infants treated with lopinavir/ritonavir have been reported; thus, lopinavir/ritonavir should not be used in this group of patients.^{20, 21} Co-administration of ritonavir with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution because it is unknown how co-administering any of these drugs with ritonavir will affect the PR interval. In addition, ritonavir should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as those with underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

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