Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Ritonavir (RTV, Norvir) (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

Oral Powder: 100 mg per packet

Oral Solution: 80 mg/mL. Oral solution contains 43% (v/v) ethanol and approximately 27% (w/v) propylene glycol.

Tablets: 100 mg

Generic Formulation

Tablets: 100 mg

Fixed-Dose Combination Solution:

- [*Kaletra*] Lopinavir 80 mg/ritonavir 20 mg/mL. Oral solution contains 42.4% (v/v) ethanol and 15.3% (w/v) propylene glycol.

Fixed-Dose Combination Tablets:

- [*Kaletra*] Lopinavir 100 mg/ritonavir 25 mg
- [*Kaletra*] Lopinavir 200 mg/ritonavir 50 mg

Dosing Recommendations

Ritonavir as a Pharmacokinetic Enhancer:[a]

- Ritonavir is used as a pharmacokinetic enhancer of other protease inhibitors (PIs). The recommended dose of ritonavir varies and is specific to the drug combination selected. See other sections of the Drug Appendix for information about the recommended doses of ritonavir to use with specific PIs.

Formulation Considerations:

- The oral solution contains propylene glycol and ethanol.
- The oral powder is preferred over the oral solution for children who cannot swallow the tablets and who need a dose of at least 100 mg, because the oral powder does not contain propylene glycol or ethanol.
- Ritonavir oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.

[*Kaletra*] Lopinavir/Ritonavir

Infant, Child, Adolescent, and Adult Dose:

- See the Lopinavir/Ritonavir section of the Drug Appendix.

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Hyperglycemia
- Fat maldistribution

Special Instructions

- Administer ritonavir with food to increase absorption and reduce the likelihood and severity of GI adverse events.
- **Do not administer** ritonavir with cobicistat or drugs that contain cobicistat (e.g., Stribild, Genvoya, Prezcobix, Evotaz).
- **Do not refrigerate** ritonavir oral solution; store at 68°F to 77°F (20°C to 25°C). Shake the solution well before use.
- Ritonavir oral powder should be mixed with a soft food (e.g., apple sauce, vanilla pudding) or a liquid (e.g., water, chocolate milk, infant formula) to help mitigate the bitter taste. Administer or discard the mixture within 2 hours of mixing.

To Increase Tolerability of Ritonavir Oral Solution in Children:

- Mix the solution with milk, chocolate milk, ice cream, or vanilla or chocolate pudding.
- Before administering ritonavir, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds. Another option is to give a child peanut butter to coat the mouth.
- After administration, give strong-tasting foods (e.g., maple syrup, cheese).
- Check a child's food allergy history before making these recommendations.
- Counsel parents or patients that the bad taste will not be completely masked.

Metabolism/Elimination

- Cytochrome P450 (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. Ritonavir inhibits the intestinal transporter P glycoprotein.

Ritonavir Dosing in Patients with Hepatic Impairment:

- Ritonavir is primarily metabolized by the liver. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. There are no data on ritonavir dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering ritonavir to patients with moderate-to-severe hepatic impairment.

[a] Ritonavir has antiviral activity, but it is not used as an antiviral agent (see text).

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

- *Metabolism:* Ritonavir is extensively metabolized by (and is one of the most potent inhibitors of) hepatic cytochrome P450 (CYP) 3A. Also, ritonavir is a CYP2D6 inhibitor and a CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. Ritonavir inhibits the intestinal transporter P glycoprotein. 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.
- Ritonavir and cobicistat **are not interchangeable**. The potential drug interactions for these drugs are different.[1]
- Avoid concomitant use of intranasal or inhaled fluticasone. Reduced elimination of steroids can increase steroid effects, leading to adrenal insufficiency.[2] Use caution when prescribing ritonavir with other

inhaled steroids. Limited data suggest that beclomethasone may be a suitable alternative to fluticasone when a patient who is taking ritonavir requires an inhaled or intranasal corticosteroid.[3,4] In one case, a patient developed iatrogenic Cushing syndrome and suppression of the hypothalamic-pituitary axis secondary to the drug interaction between ritonavir and intra-articular triamcinolone injection.[5] See Drug Interactions between Protease Inhibitors and Other Drugs in the Adult and Adolescent Antiretroviral Guidelines for additional information.

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 preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, and pancreatitis. Cases of hepatitis, including life-threatening cases, have been reported. Allergic reactions, including bronchospasm, urticaria, and angioedema. Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.[6]

Resistance

Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other antiretroviral (ARV) medications.

Pediatric Use

Approval

Ritonavir has been approved by the Food and Drug Administration for use in the pediatric population.

Effectiveness in Practice

Use of ritonavir as the sole protease inhibitor (PI) in ARV therapy in children **is not recommended**. In both children and adults, ritonavir is recommended as a PK enhancer for use with other PIs. Ritonavir is a CYP3A inhibitor and functions as a PK enhancer by slowing the metabolism of the PIs.

Dosing

Pediatric dosing regimens, including boosted darunavir, atazanavir, and the PI coformulation lopinavir/ritonavir (LPV/r), are available. For more information about individual PIs, see other sections of the Drug Appendix.

Toxicity

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir 400 mg twice daily.[6] Potentially life-threatening arrhythmias have been reported in premature newborn infants who were treated with LPV/r; the use of LPV/r **is not recommended** before a gestational age of 42 weeks.[7,8] Coadministration 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 coadministering 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 patients who have underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

References

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