Ritonavir (RTV, Norvir)

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Formulations

Oral Powder: 100 mg per packet

Tablet: 100 mg

Generic Formulation

- 100-mg tablet

Fixed-Dose Combination (FDC) Solution

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

FDC Tablets

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

When using FDC tablets or solution, refer to other sections of Appendix A. Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Ritonavir (RTV) as a Pharmacokinetic Enhancer

- RTV is used as a pharmacokinetic (PK) enhancer of other protease inhibitors (PIs). The recommended dose of RTV varies and is specific to the drug combination selected. See other sections of Appendix A. Pediatric Antiretroviral Drug Information for information about the recommended doses of RTV to use with specific PIs. RTV has antiviral activity, but it is not used as an antiviral agent; instead, it is used as a PK enhancer of other PIs.

Formulation Considerations

- RTV oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.

[Kaletra] Lopinavir/RTV

Infant, Child, Adolescent, and Adult Dose

- See the Lopinavir/Ritonavir section of Appendix A. Pediatric Antiretroviral Drug Information for information.

Selected Adverse Events

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

Special Instructions

- Administer RTV with food to increase absorption and reduce the likelihood and severity of GI adverse events.
- **Do not administer** RTV with cobicistat (COBI) or drugs that contain COBI (i.e., Evotaz, Genvoya, Prezcobix, Stribild, Symtuza).
- RTV oral powder should be mixed with a soft food (e.g., applesauce, 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 RTV Oral Powder in Children • Mix the powder with milk, chocolate milk, ice cream, or vanilla or chocolate pudding. • Before administering RTV, give a child ice chips, an ice pop, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds. Another option is to give a nonallergic child peanut butter or hazelnut chocolate spread to coat the mouth.[1] • After administration, give foods with strong tastes (e.g., maple syrup, cheese). • Check a child's food allergy history before making these recommendations. • Counsel caregivers 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. RTV inhibits the intestinal transporter P-glycoprotein. **RTV Dosing in Patients With Hepatic Impairment** • RTV is primarily metabolized by the liver. • No dose adjustment is necessary in patients with mild or moderate hepatic impairment. • No data exist 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

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

- *Metabolism:* Ritonavir (RTV) is extensively metabolized by (and is one of the most potent inhibitors of) hepatic cytochrome P450 (CYP) 3A. Also, RTV is a CYP2D6 inhibitor and a CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. RTV inhibits the intestinal transporter P-glycoprotein. There is potential for multiple drug interactions with RTV.
- Before RTV is administered, a patient's medication profile should be reviewed carefully for potential interactions with RTV and overlapping toxicities with other drugs.
- RTV and cobicistat **are not interchangeable.** The potential drug interactions for these drugs are different.[2]
- Avoid concomitant use of corticosteroids, including intranasal or inhaled fluticasone or inhaled budesonide. Reduced elimination of steroids can increase steroid effects, leading to adrenal insufficiency.[3,4] Use caution when prescribing RTV with other inhaled steroids. Limited data suggest that beclomethasone may be a suitable alternative to fluticasone when a patient who is

taking RTV requires an inhaled or intranasal corticosteroid.[5,6] Iatrogenic Cushing's syndrome and suppression of the hypothalamic-pituitary axis secondary to the drug interaction between RTV and local injection of triamcinolone has occurred.[7,8] See Table 24a. 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, abnormal lipid levels
- *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, pancreatitis. Cases of hepatitis, including life-threatening cases, have been reported. Allergic reactions, including bronchospasm, urticaria, and angioedema have occurred. Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.[9]

Resistance

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

Pediatric Use

Approval

RTV has been approved by the U.S. Food and Drug Administration for use in the pediatric population.

Effectiveness in Practice

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

Dosing

Dosing regimens for RTV-boosted darunavir and atazanavir, as well as coformulated lopinavir/ritonavir (LPV/r) are available for pediatric patients. See the Darunavir, Atazanavir, and Lopinavir/Ritonavir sections for specific guidance. For more information about individual PIs, see other sections of Appendix A: Pediatric Antiretroviral Drug Information. RTV oral solution is no longer available.

Toxicity

Full-dose RTV has been shown to prolong the PR interval in a study of healthy adults who were given RTV 400 mg twice daily.[9] Potentially life-threatening arrhythmias have been reported in premature infants who were treated with LPV/r; therefore, the use of LPV/r is generally not recommended before a gestational age of 42 weeks (see the Lopinavir/Ritonavir section).[10,11] Coadministration of RTV 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 RTV will affect the PR interval. In addition, RTV 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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