

# Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

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Ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein inhibitor, is coadministered with nirmatrelvir to increase the blood concentration of nirmatrelvir, thereby making it effective against SARS-CoV-2. Ritonavir may also increase blood concentrations of certain concomitant medications. Because ritonavir-boosted nirmatrelvir (Paxlovid) is the only highly effective oral antiviral for the treatment of COVID-19, drug interactions that can be safely managed should not preclude the use of this medication.

Clinicians should be aware that many commonly used medications can be safely coadministered with ritonavir-boosted nirmatrelvir despite its drug-drug interaction potential. Box 1 includes commonly prescribed medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.

## Box 1. Commonly Prescribed Outpatient Medications Not Expected to Have Clinically Relevant Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Medications Without Clinically Relevant Interactions		
These commonly prescribed medications may be coadministered without dose adjustment and without increased monitoring. <sup>a</sup> This list is not inclusive of all noninteracting medications within each drug category.		
<p><b>Acid reducing agents</b></p> <ul style="list-style-type: none"> <li>• Famotidine</li> <li>• Omeprazole</li> <li>• Pantoprazole</li> </ul> <p><b>Allergy medications</b></p> <ul style="list-style-type: none"> <li>• Cetirizine</li> <li>• Diphenhydramine</li> <li>• Loratadine</li> </ul> <p><b>Anti-infective agents</b></p> <ul style="list-style-type: none"> <li>• Azithromycin</li> <li>• Hydroxychloroquine</li> </ul> <p><b>Cardiovascular agents</b></p> <ul style="list-style-type: none"> <li>• Aspirin</li> <li>• Atenolol</li> <li>• Carvedilol</li> <li>• Furosemide</li> <li>• Hydrochlorothiazide</li> <li>• Irbesartan</li> <li>• Isosorbide Dinitrate</li> <li>• Lisinopril</li> <li>• Losartan</li> <li>• Metoprolol</li> <li>• Prasugrel</li> </ul>	<p><b>Diabetes medications</b></p> <ul style="list-style-type: none"> <li>• Empagliflozin</li> <li>• Insulin</li> <li>• Metformin</li> <li>• Pioglitazone</li> </ul> <p><b>Immunosuppressants</b></p> <ul style="list-style-type: none"> <li>• Methotrexate</li> <li>• Mycophenolate</li> <li>• Prednisone</li> </ul> <p><b>Lipid-modifying agents</b></p> <ul style="list-style-type: none"> <li>• Ezetimibe</li> <li>• Pitavastatin</li> <li>• Pravastatin</li> </ul> <p><b>Neuropsychiatric agents</b></p> <ul style="list-style-type: none"> <li>• Amitriptyline</li> <li>• Bupropion</li> <li>• Citalopram</li> <li>• Duloxetine</li> <li>• Escitalopram</li> <li>• Fluoxetine</li> <li>• Gabapentin</li> <li>• Lorazepam</li> <li>• Nortriptyline</li> <li>• Olanzapine</li> <li>• Paroxetine</li> <li>• Sertraline</li> <li>• Venlafaxine</li> </ul>	<p><b>Pain medications</b></p> <ul style="list-style-type: none"> <li>• Acetaminophen</li> <li>• Aspirin</li> <li>• Codeine</li> <li>• Ibuprofen</li> <li>• Naproxen</li> </ul> <p><b>Respiratory medications</b></p> <ul style="list-style-type: none"> <li>• Corticosteroids (inhaled)</li> <li>• Formoterol</li> <li>• Montelukast</li> </ul> <p><b>Miscellaneous</b></p> <ul style="list-style-type: none"> <li>• Allopurinol</li> <li>• Contraceptives (oral)<sup>b</sup></li> <li>• Donepezil</li> <li>• Enoxaparin</li> <li>• Finasteride</li> <li>• Levothyroxine</li> <li>• Ondansetron</li> </ul>

### Medications Without Clinically Relevant Interactions, continued

<sup>a</sup> This list is primarily based on the most common medication searches by U.S. users on the Liverpool COVID-19 Drug Interactions website between January 1 and April 13, 2022 (internal communication, April 2022). The Liverpool website classifies these medications as those that have no interaction or weak interaction with ritonavir-boosted nirmatrelvir.

<sup>b</sup> The Food and Drug Administration Emergency Use Authorization for ritonavir-boosted nirmatrelvir suggests that individuals who use contraceptive products containing ethinyl estradiol consider using a backup, nonhormonal contraceptive method because coadministration may result in low ethinyl estradiol levels. However, the low level is not expected to be clinically significant during 5 days of therapy. The progestin concentration of a combined hormonal contraceptive is expected to remain similar or increase with coadministration, which would maintain the effectiveness of the oral contraceptive.

### Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir

Clinicians should be aware that, in some cases, drug-drug interactions with ritonavir-boosted nirmatrelvir may lead to serious or life-threatening drug toxicities. The recommended treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. After the last dose is administered, most of the interaction potential resolves within 2 to 3 days, although resolution may take longer in elderly adults.<sup>1</sup>

Ritonavir-boosted nirmatrelvir should not be given within 2 weeks of administering a strong CYP3A4 inducer (e.g., St. John's wort, rifampin). Ritonavir-boosted nirmatrelvir is **contraindicated** in this setting, because strong CYP3A4 inducers may reduce the concentrations of nirmatrelvir and ritonavir, rendering the treatment ineffective against SARS-CoV-2. Alternative treatment for COVID-19 should be prescribed.

### Identifying Drug-Drug Interactions

Before prescribing ritonavir-boosted nirmatrelvir, carefully review the patient's concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs.

Consult 1 or more of the following resources for information on identifying and managing drug-drug interactions:

- Quick reference lists:
  - Box 1 lists commonly prescribed outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.
  - Box 2 lists medications that have clinically relevant drug-drug interactions with ritonavir-boosted nirmatrelvir.
- Web-based drug-drug interaction checker:
  - The [Liverpool COVID-19 Drug Interactions website](#)
- Tables with guidance on managing specific drug-drug interactions:
  - The [Ontario COVID-19 Science Advisory Table](#)
  - The Food and Drug Administration Emergency Use Authorization [fact sheet](#) and [checklist](#) for ritonavir-boosted nirmatrelvir

Consider expert consultation (e.g., with a pharmacist, an HIV specialist, or the patient's specialist providers), especially for patients receiving highly specialized therapies or drugs prone to concentration-dependent toxicities, such as certain anticonvulsant, anticoagulant, antiarrhythmic, chemotherapeutic, neuropsychiatric, and immunosuppressant drugs.

## Management Strategies for Drug-Drug Interactions

Consider the magnitude and significance of the potential interaction when choosing management strategies for patients who are to receive ritonavir-boosted nirmatrelvir. Potential strategies include:

- Temporarily withholding the concomitant medication,
- Increasing monitoring for potential adverse reactions to the concomitant medication,
- Adjusting the dose of the concomitant medication,
- Using an alternative to the concomitant medication, *or*
- Using alternative COVID-19 therapies (see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#)).

Use the chosen strategy for the 5-day duration of ritonavir-boosted nirmatrelvir treatment and for at least 2 to 3 days after treatment completion. The strategy may need to continue for a longer duration if ritonavir-boosted nirmatrelvir is initiated in an elderly patient or if the interacting medication has a long half-life.

### Box 2. Outpatient Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Not all medications that may interact with ritonavir-boosted nirmatrelvir are included in Box 2. Deviation from the recommended strategies may be appropriate in certain clinical scenarios.

Prescribe Alternative COVID-19 Therapy		
For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.		
<p><b>Anticonvulsants</b></p> <ul style="list-style-type: none"> <li>• Carbamazepine</li> <li>• Phenobarbital</li> <li>• Phenytoin</li> <li>• Primidone</li> </ul> <p><b>Anti-infective agents</b></p> <ul style="list-style-type: none"> <li>• Glecaprevir/pibrentasvir</li> <li>• Rifampin</li> <li>• Rifapentine</li> </ul> <p><b>Immunosuppressants</b></p> <ul style="list-style-type: none"> <li>• Voclosporin</li> </ul>	<p><b>Cardiovascular agents</b></p> <ul style="list-style-type: none"> <li>• Amiodarone</li> <li>• Clopidogrel<sup>a,b</sup></li> <li>• Disopyramide</li> <li>• Dofetilide</li> <li>• Dronedarone</li> <li>• Eplerenone</li> <li>• Flecainide</li> <li>• Ivabradine</li> <li>• Propafenone</li> <li>• Quinidine</li> </ul> <p><b>Neuropsychiatric agents</b></p> <ul style="list-style-type: none"> <li>• Clozapine</li> <li>• Lumateperone</li> <li>• Lurasidone</li> <li>• Midazolam (oral)</li> <li>• Pimozide</li> </ul>	<p><b>Pain medications</b></p> <ul style="list-style-type: none"> <li>• Meperidine (pethidine)</li> </ul> <p><b>Pulmonary hypertension medications</b></p> <ul style="list-style-type: none"> <li>• Sildenafil</li> <li>• Tadalafil</li> <li>• Vardenafil</li> </ul> <p><b>Miscellaneous</b></p> <ul style="list-style-type: none"> <li>• Bosentan</li> <li>• Certain chemotherapeutic agents<sup>c</sup></li> <li>• Ergot derivatives</li> <li>• Lumacaftor/ivacaftor</li> <li>• St. John's wort</li> <li>• Tolvaptan</li> </ul>

### Temporarily Withhold Concomitant Medication, If Clinically Appropriate

Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is elderly or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

<p><b>Anticoagulants</b></p> <ul style="list-style-type: none"> <li>• Rivaroxaban<sup>d</sup></li> </ul> <p><b>Anti-infective agents</b></p> <ul style="list-style-type: none"> <li>• Erythromycin</li> </ul> <p><b>BPH medications</b></p> <ul style="list-style-type: none"> <li>• Alfuzosin</li> <li>• Silodosin</li> </ul> <p><b>Cardiovascular agents</b></p> <ul style="list-style-type: none"> <li>• Aliskiren</li> <li>• Ranolazine</li> <li>• Ticagrelor<sup>b</sup></li> <li>• Vorapaxar</li> </ul> <p><b>Immunosuppressants<sup>f</sup></b></p> <ul style="list-style-type: none"> <li>• Everolimus</li> <li>• Sirolimus</li> <li>• Tacrolimus</li> </ul>	<p><b>Lipid-modifying agents</b></p> <ul style="list-style-type: none"> <li>• Atorvastatin<sup>e</sup></li> <li>• Lomitapide</li> <li>• Lovastatin<sup>e</sup></li> <li>• Rosuvastatin<sup>e</sup></li> <li>• Simvastatin<sup>e</sup></li> </ul> <p><b>Migraine medications</b></p> <ul style="list-style-type: none"> <li>• Eletriptan</li> <li>• Rimegepant</li> <li>• Ubrogapant</li> </ul> <p><b>Neuropsychiatric agents</b></p> <ul style="list-style-type: none"> <li>• Clonazepam<sup>g</sup></li> <li>• Clorazepate<sup>g</sup></li> <li>• Diazepam<sup>g</sup></li> <li>• Estazolam<sup>g</sup></li> <li>• Flurazepam<sup>g</sup></li> <li>• Suvorexant</li> <li>• Triazolam<sup>g</sup></li> </ul>	<p><b>Erectile dysfunction medications</b></p> <ul style="list-style-type: none"> <li>• Avanafil</li> </ul> <p><b>Respiratory medications</b></p> <ul style="list-style-type: none"> <li>• Salmeterol</li> </ul> <p><b>Miscellaneous</b></p> <ul style="list-style-type: none"> <li>• Certain chemotherapeutic agents<sup>c</sup></li> <li>• Colchicine<sup>h</sup></li> <li>• Finerenone</li> <li>• Flibanserin</li> <li>• Naloxegol</li> </ul>
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### Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the [Liverpool COVID-19 Drug Interactions website](#) or the [Ontario COVID-19 Science Advisory Table](#) for specific dosing recommendations.<sup>i</sup> If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.

<p><b>Anticoagulants</b></p> <ul style="list-style-type: none"> <li>• Apixaban</li> <li>• Dabigatran</li> <li>• Edoxaban</li> </ul> <p><b>Anti-infective agents</b></p> <ul style="list-style-type: none"> <li>• Clarithromycin</li> <li>• Itraconazole</li> <li>• Ketoconazole</li> <li>• Maraviroc</li> <li>• Rifabutin</li> </ul> <p><b>BPH medications</b></p> <ul style="list-style-type: none"> <li>• Tamsulosin</li> </ul> <p><b>Cardiovascular agents</b></p> <ul style="list-style-type: none"> <li>• Cilostazol</li> <li>• Digoxin</li> <li>• Mexiletine</li> </ul> <p><b>Diabetes medications</b></p> <ul style="list-style-type: none"> <li>• Saxagliptin</li> </ul>	<p><b>Erectile dysfunction medications</b></p> <ul style="list-style-type: none"> <li>• Sildenafil</li> <li>• Tadalafil</li> <li>• Vardenafil</li> </ul> <p><b>Immunosuppressants<sup>f</sup></b></p> <ul style="list-style-type: none"> <li>• Cyclosporine</li> </ul> <p><b>Neuropsychiatric agents</b></p> <ul style="list-style-type: none"> <li>• Alprazolam<sup>g</sup></li> <li>• Aripiprazole</li> <li>• Brexpiprazole</li> <li>• Buspirone</li> <li>• Cariprazine</li> <li>• Chlordiazepoxide<sup>g</sup></li> <li>• Clobazam<sup>g</sup></li> <li>• Iloperidone</li> <li>• Pimavanserin</li> <li>• Quetiapine</li> <li>• Trazodone</li> </ul>	<p><b>Pain medications</b></p> <ul style="list-style-type: none"> <li>• Fentanyl</li> <li>• Hydrocodone</li> <li>• Oxycodone</li> </ul> <p><b>Pulmonary hypertension medications</b></p> <ul style="list-style-type: none"> <li>• Riociguat</li> </ul> <p><b>Miscellaneous</b></p> <ul style="list-style-type: none"> <li>• Certain chemotherapeutic agents<sup>c</sup></li> <li>• Darifenacin</li> <li>• Elexacaftor/tezacaftor/ivacaftor</li> <li>• Eluxadoline</li> <li>• Ivacaftor</li> <li>• Tezacaftor/ivacaftor</li> </ul>
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### Continue Concomitant Medication and Monitor for Adverse Effects

Pre-emptive dose adjustment is not required but may be considered. Educate patients on potential adverse effects. Consult the [Liverpool COVID-19 Drug Interactions website](#) or the [Ontario COVID-19 Science Advisory Table](#) for monitoring guidance and dose adjustment information if needed.<sup>i</sup>

<p><b>Anticoagulants</b></p> <ul style="list-style-type: none"> <li>• Warfarin</li> </ul> <p><b>Anti-infective agents</b></p> <ul style="list-style-type: none"> <li>• Cobicistat or ritonavir-boosted antiretrovirals</li> <li>• Isavuconazole</li> <li>• Posaconazole</li> <li>• Voriconazole</li> </ul> <p><b>BPH medications</b></p> <ul style="list-style-type: none"> <li>• Doxazosin</li> <li>• Terazosin</li> </ul> <p><b>Diabetes medications</b></p> <ul style="list-style-type: none"> <li>• Glyburide</li> </ul>	<p><b>Cardiovascular agents</b></p> <ul style="list-style-type: none"> <li>• Amlodipine</li> <li>• Diltiazem</li> <li>• Felodipine</li> <li>• Nifedipine</li> <li>• Sacubitril</li> <li>• Valsartan</li> <li>• Verapamil</li> </ul> <p><b>Neuropsychiatric agents</b></p> <ul style="list-style-type: none"> <li>• Haloperidol</li> <li>• Hydroxyzine</li> <li>• Mirtazapine</li> <li>• Risperidone</li> <li>• Ziprasidone</li> <li>• Zolpidem</li> </ul>	<p><b>Pain medications</b></p> <ul style="list-style-type: none"> <li>• Buprenorphine</li> <li>• Hydromorphone</li> <li>• Methadone</li> <li>• Morphine</li> <li>• Tramadol</li> </ul>
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<sup>a</sup> Reduced effectiveness of clopidogrel is likely. It may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

<sup>b</sup> For patients at very high risk of thrombosis (e.g., received a coronary stent within the past 6 weeks), consider prescribing an alternative antiplatelet (e.g., prasugrel) or an alternative COVID-19 therapy.

<sup>c</sup> Ritonavir-boosted nirmatrelvir may increase concentrations of some chemotherapeutic agents, leading to an increased potential for drug toxicities. Some chemotherapeutic agents may decrease the effectiveness of ritonavir-boosted nirmatrelvir. Please refer to the FDA EUA ritonavir-boosted nirmatrelvir fact sheet and the prescribing information for the chemotherapeutic agent and consult the patient's specialist provider. [The University Health Network/Kingston Health Sciences Centre](#) is an additional resource for evaluating drug-drug interactions for chemotherapeutic agents.

<sup>d</sup> For patients at high risk of arterial or venous thrombosis (e.g., had a stroke within the past 3 months with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 7–9 or a pulmonary embolism within the past month), consult the primary or specialty provider and consider using an alternative anticoagulant or COVID-19 therapy.

<sup>e</sup> For lovastatin and simvastatin, withhold at least 12 hours before initiation of ritonavir-boosted nirmatrelvir, during treatment, and for 5 days after treatment completion. For atorvastatin and rosuvastatin, withhold at the beginning of treatment with ritonavir-boosted nirmatrelvir and resume after completion of the 5-day course. If withholding a statin is not clinically appropriate (e.g., the patient had a recent myocardial infarction), the doses of atorvastatin and rosuvastatin can be adjusted and continued, and lovastatin and simvastatin should be switched to an alternative statin.

<sup>f</sup> Consult a patient's specialist providers before coadministering these immunosuppressants and ritonavir-boosted nirmatrelvir. These immunosuppressants have significant drug-drug interaction potential with ritonavir, and close monitoring may not be feasible. Alternative COVID-19 therapy may need to be considered. See the [American Society of Transplantation statement](#) for more information.

<sup>g</sup> Abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate an acute withdrawal reaction.<sup>2</sup> The risk is greatest for patients who have been using high doses of benzodiazepines over an extended period.

<sup>h</sup> For patients with severe hepatic or renal impairment, coadministration of colchicine and ritonavir-boosted nirmatrelvir is **contraindicated** due to the potential for serious or life-threatening reactions.

<sup>i</sup> For medications not included on the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table, refer to the medication's FDA label for information on coadministration with ritonavir or other strong CYP3A4 and/or P-gp inhibitors.

**Key:** BPH = benign prostatic hyperplasia; CHA<sub>2</sub>DS<sub>2</sub>-VASc = congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; CYP = cytochrome P450; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; P-gp = P-glycoprotein

## References

1. Stader F, Khoo S, Stoeckle M, et al. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. *J Antimicrob Chemother.* 2020;75(10):3084-3086. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32556272>.
2. Food and Drug Administration. FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. 2020. Available at: <https://www.fda.gov/media/142368/download>.