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)

<table>
<thead>
<tr>
<th>Medications Without Clinically Relevant Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>These commonly prescribed medications may be coadministered without dose adjustment and without increased monitoring. This list is not inclusive of all noninteracting medications within each drug category.</td>
</tr>
<tr>
<td><strong>Acid reducing agents</strong></td>
</tr>
<tr>
<td>• Famotidine</td>
</tr>
<tr>
<td>• Omeprazole</td>
</tr>
<tr>
<td>• Pantoprazole</td>
</tr>
<tr>
<td><strong>Allergy medications</strong></td>
</tr>
<tr>
<td>• Cetirizine</td>
</tr>
<tr>
<td>• Diphenhydramine</td>
</tr>
<tr>
<td>• Loratadine</td>
</tr>
<tr>
<td><strong>Anti-infective agents</strong></td>
</tr>
<tr>
<td>• Azithromycin</td>
</tr>
<tr>
<td>• Hydroxychloroquine</td>
</tr>
<tr>
<td><strong>Cardiovascular agents</strong></td>
</tr>
<tr>
<td>• Aspirin</td>
</tr>
<tr>
<td>• Atenolol</td>
</tr>
<tr>
<td>• Carvedilol</td>
</tr>
<tr>
<td>• Furosemide</td>
</tr>
<tr>
<td>• Hydrochlorothiazide</td>
</tr>
<tr>
<td>• Irbesartan</td>
</tr>
<tr>
<td>• Isosorbide Dinitrate</td>
</tr>
<tr>
<td>• Lisinopril</td>
</tr>
<tr>
<td>• Losartan</td>
</tr>
<tr>
<td>• Metoprolol</td>
</tr>
<tr>
<td>• Prasugrel</td>
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</tr>
</tbody>
</table>
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.1

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.

<table>
<thead>
<tr>
<th>Prescribe Alternative COVID-19 Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.</td>
</tr>
</tbody>
</table>

**Anticonvulsants**
- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

**Anti-infective agents**
- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

**Immunosuppressants**
- Voclosporin

**Cardiovascular agents**
- Amiodarone
- Clopidogrel
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide
- Ivabradine
- Propafenone
- Quinidine

**Neuropsychiatric agents**
- Clozapine
- Lumateperone
- Lurasidone
- Midazolam (oral)
- Pimozide

**Pain medications**
- Meperidine (pethidine)

**Pulmonary hypertension medications**
- Sildenafil
- Tadalafil
- Vardenafil

**Miscellaneous**
- Bosentan
- Certain chemotherapeutic agents
- Ergot derivatives
- Lumacaftor/ivacaftor
- St. John's wort
- Tolvaptan
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.

### Anticoagulants
- Rivaroxaban
- Apixaban
- Dabigatran
- Edoxaban
- Elixiritinib
- Tinzaparin

### Anti-infective agents
- Erythromycin
- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Tenofovir

### BPH medications
- Alfuzosin
- Silodosin
- Tamsulosin

### Cardiovascular agents
- Aliskiren
- Cilostazol
- Digoxin
- Mexiletine
- Ranolazine
- Ticagrelor
- Verapamil

### Immunosuppressants
- Everolimus
- Sirolimus
- Tacrolimus
- Ciclosporin
- Eculizumab
- Belatacept
- Belimumab

### Lipid-modifying agents
- Atorvastatin
- Lomitapide
- Lovastatin
- Rosuvastatin
- Simvastatin
- Ezetimibe
- Cholesteryl ester transfer protein (CETP) inhibitors

### Migraine medications
- Emeprizole
- Rimegepant
- Ubogepant

### Neuropsychiatric agents
- Clonazepam
- Clorazepate
- Diazepam
- Estazolam
- Flurazepam
- Suvorexant
- Triazolam

### Erectile dysfunction medications
- Sildenafil
- Tadalafil
- Vardenafil

### Pain medications
- Fentanyl
- Hydrocodone
- Oxycodone

### Pulmonary hypertension medications
- Riociguat

### Miscellaneous
- Certain chemotherapeutic agents
- Darifenacin
- Elexacaftor/tezacaftor/ivacaftor
- Eluxadoline
- Ivacaftor
- Tezacaftor/ivacaftor
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.1

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>Cardiovascular agents</th>
<th>Pain medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Warfarin</td>
<td>• Amlodipine</td>
<td>• Buprenorphine</td>
</tr>
<tr>
<td><strong>Anti-infective agents</strong></td>
<td>• Diltiazem</td>
<td>• Hydromorphone</td>
</tr>
<tr>
<td>• Cobicistat or ritonavir-boosted antiretrovirals</td>
<td>• Felodipine</td>
<td>• Methadone</td>
</tr>
<tr>
<td>• Isavuconazole</td>
<td>• Nifedipine</td>
<td>• Morphine</td>
</tr>
<tr>
<td>• Posaconazole</td>
<td>• Sacubitril</td>
<td>• Tramadol</td>
</tr>
<tr>
<td>• Voriconazole</td>
<td>• Valsartan</td>
<td></td>
</tr>
<tr>
<td><strong>BPH medications</strong></td>
<td>• Verapamil</td>
<td></td>
</tr>
<tr>
<td>• Doxazosin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Terazosin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Glyburide</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuropsychiatric agents</th>
<th>Pain medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Haloperidol</td>
<td>• Buprenorphine</td>
</tr>
<tr>
<td>• Hydroxyzine</td>
<td>• Hydromorphone</td>
</tr>
<tr>
<td>• Mirtazapine</td>
<td>• Methadone</td>
</tr>
<tr>
<td>• Risperidone</td>
<td>• Morphine</td>
</tr>
<tr>
<td>• Ziprasidone</td>
<td>• Tramadol</td>
</tr>
<tr>
<td>• Zolpidem</td>
<td></td>
</tr>
</tbody>
</table>

**Anticoagulants**

- Warfarin

**Anti-infective agents**

- Cobicistat or ritonavir-boosted antiretrovirals
- Isavuconazole
- Posaconazole
- Voriconazole

**BPH medications**

- Doxazosin
- Terazosin

**Diabetes medications**

- Glyburide

**Cardiovascular agents**

- Amlodipine
- Diltiazem
- Felodipine
- Nifedipine
- Sacubitril
- Valsartan
- Verapamil

**Neuropsychiatric agents**

- Haloperidol
- Hydroxyzine
- Mirtazapine
- Risperidone
- Ziprasidone
- Zolpidem

**Pain medications**

- Buprenorphine
- Hydromorphone
- Methadone
- Morphine
- Tramadol

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a 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.

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

c 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.

d For patients at high risk of arterial or venous thrombosis (e.g., had a stroke within the past 3 months with a CHA2DS2-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.

e 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.

f 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.

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

h 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.

i 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; CHA2DS2-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

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](https://www.fda.gov/media/142368/download).