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)

<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acid reducing agents</th>
<th>Diabetes medications</th>
<th>Pain medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Famotidine</td>
<td>• Empagliflozin</td>
<td>• Acetaminophen</td>
</tr>
<tr>
<td>• Omeprazole</td>
<td>• Insulin</td>
<td>• Aspirin</td>
</tr>
<tr>
<td>• Pantoprazole</td>
<td>• Metformin</td>
<td>• Codeine</td>
</tr>
<tr>
<td><strong>Allergy medications</strong></td>
<td>• Pioglitazone</td>
<td>• Ibuprofen</td>
</tr>
<tr>
<td>• Cetirizine</td>
<td><strong>Immunosuppressants</strong></td>
<td>• Naproxen</td>
</tr>
<tr>
<td>• Diphenhydramine</td>
<td>• Methotrexate</td>
<td><strong>Respiratory medications</strong></td>
</tr>
<tr>
<td>• Loratadine</td>
<td>• Mycophenolate</td>
<td>• Corticosteroids (inhaled)</td>
</tr>
<tr>
<td><strong>Anti-infective agents</strong></td>
<td>• Prednisone</td>
<td>• Formoterol</td>
</tr>
<tr>
<td>• Azithromycin</td>
<td><strong>Lipid-modifying agents</strong></td>
<td>• Montelukast</td>
</tr>
<tr>
<td>• Hydroxychloroquine</td>
<td>• Ezetimibe</td>
<td><strong>Miscellaneous</strong></td>
</tr>
<tr>
<td><strong>Cardiovascular agents</strong></td>
<td>• Pitavastatin</td>
<td>• Alopurinol</td>
</tr>
<tr>
<td>• Aspirin</td>
<td>• Pravastatin</td>
<td>• Contraceptives (oral)</td>
</tr>
<tr>
<td>• Atenolol</td>
<td><strong>Neuropsychiatric agents</strong></td>
<td>• Donepezil</td>
</tr>
<tr>
<td>• Carvedilol</td>
<td>• Amitriptyline</td>
<td>• Enoxaparin</td>
</tr>
<tr>
<td>• Furosemide</td>
<td>• Bupropion</td>
<td>• Finasteride</td>
</tr>
<tr>
<td>• Hydrochlorothiazide</td>
<td>• Citalopram</td>
<td>• Levothyroxine</td>
</tr>
<tr>
<td>• Irbesartan</td>
<td>• Duloxetine</td>
<td>• Ondansetron</td>
</tr>
<tr>
<td>• Isosorbide Dinitrate</td>
<td>• Escitalopram</td>
<td></td>
</tr>
<tr>
<td>• Lisinopril</td>
<td>• Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>• Losartan</td>
<td>• Gabapentin</td>
<td></td>
</tr>
<tr>
<td>• Metoprolol</td>
<td>• Lorazepam</td>
<td></td>
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<tr>
<td>• Prasugrel</td>
<td>• Nortriptyline</td>
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<tr>
<td></td>
<td>• Olanzapine</td>
<td></td>
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<tr>
<td></td>
<td>• Paroxetine</td>
<td></td>
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<tr>
<td></td>
<td>• Sertraline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Venlafaxine</td>
<td></td>
</tr>
</tbody>
</table>

**Diabetes medications** | **Pain medications** |
|• Empagliflozin | • Acetaminophen |
|• Insulin | • Aspirin |
|• Metformin | • Codeine |
|• Pioglitazone | • Ibuprofen |

**Immunosuppressants** | **Respiratory medications** |
|• Methotrexate | • Corticosteroids (inhaled) |
|• Mycophenolate | • Formoterol |
|• Prednisone | • Montelukast |

**Lipid-modifying agents** |
|• Ezetimibe |
|• Pitavastatin |
|• Pravastatin |

**Neuropsychiatric agents** |
|• Amitriptyline |
|• Bupropion |
|• Citalopram |
|• Duloxetine |
|• Escitalopram |
|• Fluoxetine |
|• Gabapentin |
|• Lorazepam |
|• Nortriptyline |
|• Olanzapine |
|• Paroxetine |
|• Sertraline |
|• Venlafaxine |

**Miscellaneous** |
|• Alopurinol |
|• Contraceptives (oral) |
|• Donepezil |
|• Enoxaparin |
|• Finasteride |
|• Levothyroxine |
|• Ondansetron |

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### 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.

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*Note: The information provided is a summary of the guidelines. For detailed guidance, consult the official COVID-19 Treatment Guidelines published by NIH.*
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: Prescribe Alternative COVID-19 Therapy

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Cardiovascular agents</th>
<th>Pain medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Amiodarone</td>
<td>Meperidine (pethidine)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Clopidogrel&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Disopyramide</td>
<td>Tadalafil</td>
</tr>
<tr>
<td>Primidone</td>
<td>Dofetilide</td>
<td>Vardenafil</td>
</tr>
</tbody>
</table>

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

**Immunosuppressants**
- Voclosporin

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

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

**Miscellaneous**
- Bosentan
- Certain chemotherapeutic agents<sup>3</sup>
- Ergot derivatives
- Lumacaftor/ivacaftor
- St. John's wort
- Tolvaptan
**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.

### Anticoagulants
- Rivaroxaban<sup>2</sup>

### Anti-infective agents
- Erythromycin

### BPH medications
- Alfuzosin
- Silodosin

### Cardiovascular agents
- Aliksiren
- Ranolazine
- Ticagrelor<sup>6</sup>
- Vorapaxar

### Immunosuppressants<sup>4</sup>
- Everolimus
- Sirolimus
- Tacrolimus

### Lipid-modifying agents
- Atorvastatin<sup>e</sup>
- Lomitapide
- Lovastatin<sup>e</sup>
- Rosuvastatin<sup>e</sup>
- Simvastatin<sup>e</sup>

### Migraine medications
- Eletriptan
- Rimegepant
- Ubrogepant

### Neuropsychiatric agents
- Clonazepam<sup>9</sup>
- Clorazepate<sup>9</sup>
- Diazepam<sup>9</sup>
- Estazolam<sup>9</sup>
- Flurazepam<sup>9</sup>
- Suvorexant
- Triazolam<sup>9</sup>

### Erectile dysfunction medications
- Avanafil

### Respiratory medications
- Salmeterol

### Miscellaneous
- Certain chemotherapeutic agents<sup>c</sup>
- Colchicine<sup>a</sup>
- Finerenone
- Fibanserin
- Naloxegol

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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.

### Anticoagulants
- Apixaban
- Dabigatran
- Edoxaban

### Anti-infective agents
- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Rifabutin

### BPH medications
- Tamsulosin

### Cardiovascular agents
- Cilostazol
- Digoxin
- Mexiletine

### Diabetes medications
- Saxagliptin

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

### Immunosuppressants<sup>4</sup>
- Cyclosporine

### Neuropsychiatric agents
- Alprazolam<sup>9</sup>
- Aripiprazole
- Brexpiprazole
- Buspirone
- Cariprazine
- Chlordiazepoxide<sup>9</sup>
- Clobazam<sup>9</sup>
- Iloperidone
- Pimavanserin
- Quetiapine
- Trazodone

### Pain medications
- Fentanyl
- Hydrocodone
- Oxycodone

### Pulmonary hypertension medications
- Riociguat

### Miscellaneous
- Certain chemotherapeutic agents<sup>c</sup>
- Darifenacin
- Elexacaftor/tezacaftor/ivacaftor
- Eluxadoline
- Ivacaftor
- Tezacaftor/ivacaftor
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.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</td>
<td>• Felodipine</td>
<td>• Methadone</td>
</tr>
<tr>
<td>antiretrovirals</td>
<td>• Nifedipine</td>
<td>• Morphine</td>
</tr>
<tr>
<td>• Isavuconazole</td>
<td>• Sacubitril</td>
<td>• Tramadol</td>
</tr>
<tr>
<td>• Posaconazole</td>
<td>• Valsartan</td>
<td></td>
</tr>
<tr>
<td>• Voriconazole</td>
<td>• Verapamil</td>
<td></td>
</tr>
</tbody>
</table>

**BPH medications**

• Doxazosin
• Terazosin

**Diabetes medications**

• Glyburide

**Neuropsychiatric agents**

• Haloperidol
• Hydroxyzine
• Mirtazapine
• Risperidone
• Ziprasidone
• Zolpidem

**Cardiovascular agents**

• Amlodipine
• Diltiazem
• Felodipine
• Nifedipine
• Sacubitril
• Valsartan
• Verapamil

**Pain medications**

• Buprenorphine
• Hydromorphone
• Methadone
• Morphine
• Tramadol

¹ 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.

² For patients at very high risk of thrombosis (e.g., received a coronary stent within the past 6 weeks), consider prescribing an alternative antplatelet (e.g., prasugrel) or an alternative COVID-19 therapy.

³ 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.

⁴ 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.

⁵ 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.

⁶ 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.

⁷ Abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate an acute withdrawal reaction.² The risk is greatest for patients who have been using high doses of benzodiazepines over an extended period.

⁸ 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.

⁹ 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
References
