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 (P-gp) 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. The Food and Drug Administration (FDA) prescribing information includes a boxed warning about significant drug-drug interactions between ritonavir-boosted nirmatrelvir (Paxlovid) and other medications.

Before prescribing ritonavir-boosted nirmatrelvir to treat patients with mild to moderate COVID-19, carefully review the patient's concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs. Clinicians should consider the potential benefits of treatment with ritonavir-boosted nirmatrelvir, the potential risks of drug-drug interactions, and whether any risks related to drug-drug interactions can be safely managed. 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.

Because ritonavir-boosted nirmatrelvir 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.

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

This list is primarily based on the most common medication searches by U.S. users on the Liverpool COVID-19 Drug Interactions website.

Medications Without Clinically Relevant Interactions

These medications do not require dose adjustments when coadministered with ritonavir-boosted nirmatrelvir, and the patients do not require additional monitoring. This list does not include all the noninteracting medications within each drug category.

Acid Reducers
- Famotidine
- Omeprazole
- Pantoprazole

Allergy
- Cetirizine
- Diphenhydramine
- Fexofenadine
- Loratadine

Anti-Infectives
- Azithromycin
- Cidofovir
- Hydroxychloroquine
- Tecovirimat
- Valacyclovir

Cardiovascular
- Aspirin
- Atenolol
- Carvedilol
- Furosemide
- Hydrochlorothiazide
- Irbesartan
- Isosorbide dinitrate
- Lisinopril
- Losartan
- Metoprolol
- Prasugrel

Diabetes
- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

Immunosuppressants
- Abrocitinib
- Baricitinib
- Methotrexate
- Mycophenolate
- Prednisone

Lipid-Modifiers
- Ezetimibe
- Pitavastatin
- Pravastatin

Migraine
- Frovatriptan
- Naratriptan
- Rizatriptan
- Sumatriptan
- Zavegepant

Neuropsychiatric
- Amitriptyline
- Bupropion

Neuropsychiatric, cont'd
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Gabapentin
- Lorazepam
- Nortriptyline
- Olanzapine
- Paroxetine
- Sertraline
- Venlafaxine

Pain
- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Meloxicam
- Naproxen

Respiratory
- Corticosteroids (inhaled/nasal)
- Formoterol
- Montelukast

Miscellaneous
- Allopurinol
- Contraceptives (PO)[a]
- Cyclobenzaprine
- Donepezil
- Enoxaparin
- Finasteride
- Levothyroxine
- Most mAb products[b]
- Ondansetron

Medications Without Clinically Relevant Interactions, continued
[a] Coadministering contraceptive products that contain ethinyl estradiol with ritonavir-boosted nirmatrelvir may result in lower ethinyl estradiol concentrations. The FDA prescribing information for ritonavir-boosted nirmatrelvir suggests that individuals who use these types of contraceptive products should consider using an additional, nonhormonal contraceptive method. However, the lower ethinyl estradiol concentrations are not expected to be clinically significant during the 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 PO contraceptive.
[b] Ritonavir-boosted nirmatrelvir interacts with certain conjugated mAbs, such as ado-trastuzumab emtansine, mirvetuximab soravtansine, brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated mAbs, refer to the drug's FDA prescribing information and consult the patient's specialist providers as needed.
Key: FDA = Food and Drug Administration; mAb = monoclonal antibody; PO = oral

Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

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. CYP3A4 inhibition occurs rapidly, with maximum inhibition occurring within 48 hours of ritonavir initiation.[1] After treatment is completed and ritonavir is discontinued, 70% to 90% of CYP3A4 inhibition resolves within 2 to 3 days.[2] The time to resolution of inhibition varies based on factors such as the patient's age; therefore, resolution may take longer in some individuals, such as in adults of advanced age.

Ritonavir is also an inhibitor of CYP2D6, P-gp, and organic anion transporting polypeptide (OATP) 1B1. When used for longer durations or chronically, ritonavir may induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and uridine diphosphate-glucuronyltransferase (UGT).

Nirmatrelvir and ritonavir are CYP3A4 substrates. 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 the delayed offset of enzyme induction may reduce the concentrations of nirmatrelvir and ritonavir, rendering the treatment ineffective against SARS-CoV-2. An alternative treatment for COVID-19 should be prescribed.

Identifying Drug-Drug Interactions

Consult the following resources for information on identifying and managing drug-drug interactions.

- Quick reference lists:
  - Box 1 above lists select outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.
  - Box 2 below lists select outpatient 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 University of Waterloo/University of Toronto drug interaction guide for ritonavir-boosted nirmatrelvir
  - The FDA prescribing information for ritonavir-boosted nirmatrelvir

Management Strategies for Drug-Drug Interactions

Consider the magnitude and significance of the potential drug-drug interaction when choosing management strategies for patients who will be receiving ritonavir-boosted nirmatrelvir. Potential strategies include:

- Increasing monitoring for potential adverse effects to the concomitant medication.
- Adjusting the dose of the concomitant medication.
- Temporarily withholding the concomitant medication.
- Using an alternative to the concomitant medication.
- Using alternative COVID-19 therapies (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Use the chosen strategy for the 5-day treatment course of ritonavir-boosted nirmatrelvir 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 adult of advanced age or if the interacting medication has a long half-life.

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

The decision to prescribe ritonavir-boosted nirmatrelvir to patients who are receiving calcineurin and mammalian target of rapamycin inhibitors should always be made in consultation with the patient's specialist providers. Among reports submitted to the FDA Adverse Event Reporting System, the most commonly reported concomitant medications that resulted in serious adverse reactions, including fatal events, were calcineurin inhibitors (e.g., tacrolimus).[3] Ritonavir-boosted nirmatrelvir may be prescribed to certain patients who are receiving these medications if an expert in managing the interaction is available and close therapeutic drug monitoring is logistically feasible. Otherwise, an alternative therapy for COVID-19 should be considered. See the American Society of Transplantation statement for more information.

Interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents should also be managed in consultation with the patient's specialist providers. For guidance on managing these interactions, refer to the FDA prescribing information for ritonavir-boosted nirmatrelvir and the prescribing information for the chemotherapeutic agent. The University Health Network/Kingston Health Sciences Centre provides an additional resource for evaluating drug-drug interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents.

Patients should be counseled about ritonavir-boosted nirmatrelvir's drug-drug interaction potential and the signs and symptoms of potential adverse effects. If ritonavir-boosted nirmatrelvir is prescribed to patients who take certain recreational drugs, those patients will require counseling and careful monitoring for adverse effects.

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

The guidance in Box 2 is based on the drug-drug interaction potential of the FDA-approved, 5-day course of ritonavir-boosted nirmatrelvir.

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.

Anticonvulsants
- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

Anti-Infectives
- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

Immunosuppressants
- Voclosporin

Cardiovascular
- Amiodarone
- Clopidogrel[a,b]
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide
- Ivabradine
- Propafenone
- Quinidine

Neuropsychiatric
- Clozapine
- Lurasidone
- Midazolam (PO)
- Pimozide

Pulmonary Hypertension[c]
- Sildenafil
- Tadalafil
- Vardenafil

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

Temporarily Withhold Concomitant Medication, if Clinically Appropriate

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

Anticoagulants
- Rivaroxaban[e]

Anti-Infectives
- Erythromycin

BPH
- Alfuzosin
- Silodosin

Cardiovascular
- Aliskiren
- Ranolazine
- Ticagrelor[b]
- Vorapaxar

Immunosuppressants[f]
- Everolimus
- Sirolimus
- Tacrolimus

Lipid-modifiers
- Atorvastatin[g]
- Lomitapide
- Lovastatin[g]
- Rosuvastatin[g]
- Simvastatin[g]

Migraine
- Eletriptan
- Rimegepant
- Ubrogepant

Neuropsychiatric
- Daridorexant
- Lemborexant
- Suvorexant
- Triazolam[h]

Erectile Dysfunction
- Avanafil

Respiratory
- Salmeterol

Miscellaneous
- Certain chemotherapeutic agents[d]
- Colchicine[i]
- Finerenone
- Flibanserin
- Naloxegol

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Reduce the dose and/or extend the dosing interval of the concomitant medication. Consult the Liverpool COVID-19 Drug Interactions website or the University of Waterloo/University of Toronto drug interaction guide for specific dosing recommendations.[j] 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-Infectives
- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Rifabutin

BPH
- Tamsulosin

Cardiovascular
- Amlodipine
- Cilostazol
- Digoxin
- Diltiazem
- Felodipine
- Nifedipine
- Verapamil

Diabetes
- Saxagliptin

Erectile Dysfunction[c]
- Sildenafil
- Tadalafil
- Vardenafil

Immunosuppressants
- Cyclosporine[f]
- Dexamethasone[k]
- Fedratinib
- Ruxolitinib
- Tofacitinib
- Upadacitinib

Migraine
- Almotriptan[i]

Neuropsychiatric
- Alprazolam[h]
- Aripiprazole
- Brexpiprazole

Neuropsychiatric, cont'd
- Buspirone
- Cariprazine
- Chlordiazepoxide[h]
- Clobazam[h]
- Clonazepam[h]
- Clorazepate[h]
- Diazepam[h]
- Estazolam[h]
- Flurazepam[h]
- Iloperidone
- Lumateperone
- Pimavanserin
- Quetiapine
- Trazodone

Adjust Concomitant Medication Dose and Monitor for Adverse Effects, continued			
Pain • Fentanyl • Hydrocodone • Oxycodone **Pulmonary Hypertension** • Riociguat	**Miscellaneous** • Certain chemotherapeutic agents[d] • Darifenacin	**Miscellaneous**, cont'd • Elexacaftor/ tezacaftor/ivacaftor • Eluxadoline • Ivacaftor	**Miscellaneous**, cont'd • Solifenacin • Tezacaftor/ivacaftor
Continue Concomitant Medication and Monitor for Adverse Effects			
There is no need to pre-emptively adjust the doses of these drugs, but dose adjustments may be considered in patients with a high risk of AEs. Educate patients about potential AEs. Consult the Liverpool COVID-19 Drug Interactions website or the University of Waterloo/University of Toronto drug interaction guide for monitoring guidance and dose adjustment information.[j]			
Anticoagulants • Warfarin **Anti-Infectives** • Brincidofovir[l] • Cobicistat- or ritonavir-boosted ARV drugs • Isavuconazole • Posaconazole • Voriconazole	**BPH** • Doxazosin • Terazosin **Diabetes** • Glyburide **Cardiovascular** • Mexiletine • Sacubitril • Valsartan	**Migraine** • Zolmitriptan **Neuropsychiatric** • Haloperidol • Hydroxyzine • Mirtazapine • Risperidone • Ziprasidone • Zolpidem	**Pain** • Buprenorphine • Hydromorphone • Methadone • Morphine • Tramadol **Miscellaneous** • Certain chemotherapeutic agents[d] • Certain conjugated mAbs[m] • Oxybutynin

[a] Reduced effectiveness of clopidogrel is likely. It may be acceptable to continue using clopidogrel if the benefits of using ritonavir-boosted nirmatrelvir outweigh the risk of reduced clopidogrel effectiveness.

[b] For patients with a very high risk of thrombosis (e.g., those who received a coronary stent within the past 6 weeks), consider prescribing an alternative antiplatelet (e.g., prasugrel, if clinically appropriate) or an alternative COVID-19 therapy.

[c] Some PDE5 inhibitors are used to treat both PAH and erectile dysfunction; however, the doses used to treat PAH are higher than those used for erectile dysfunction. Because of this, and because PDE5 inhibitors are used chronically in patients with PAH, coadministration with ritonavir-boosted nirmatrelvir is **contraindicated** in these patients. PDE5 inhibitors can be coadministered with ritonavir-boosted nirmatrelvir in patients with erectile dysfunction, though the dose of the PDE5 inhibitor should be adjusted.

[d] 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 prescribing information for ritonavir-boosted nirmatrelvir 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.

[e] For patients with a high risk of arterial or venous thrombosis (e.g., those who had a stroke within the past 3 months with a CHA_2DS_2-VASc score of 7–9 or a pulmonary embolism within the past month), consult the patient's primary or specialty provider and consider using an alternative anticoagulant (e.g., LMWH) or an alternative COVID-19 therapy. For patients with a lower risk of arterial or venous thrombosis, clinicians may consider administering low-dose aspirin while rivaroxaban is being withheld.

[f] The use of another COVID-19 therapy may need to be considered. These immunosuppressants have significant drug-drug interaction potential with ritonavir, and they **should not be used** if close monitoring, including therapeutic drug monitoring (i.e., measuring drug concentrations), is not feasible. Consult the patient's specialist providers before coadministering these immunosuppressants with ritonavir-boosted nirmatrelvir. See the American Society of Transplantation statement for more information.

[g] Withhold lovastatin and simvastatin for at least 12 hours before initiating ritonavir-boosted nirmatrelvir, during treatment, and for 5 days after treatment completion. Withhold atorvastatin and rosuvastatin at the beginning of treatment with ritonavir-boosted nirmatrelvir and resume after completing the 5-day course. If withholding a statin is not clinically appropriate (e.g., because the patient recently had a myocardial infarction), clinicians can reduce the doses of

Continue Concomitant Medication and Monitor for Adverse Effects, continued

atorvastatin and rosuvastatin and continue treatment. However, lovastatin and simvastatin should be switched to an alternative statin.

[h] The guidance on managing drug-drug interactions between certain benzodiazepines and ritonavir-boosted nirmatrelvir can vary significantly between product information resources. Note that abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate an acute withdrawal reaction.[4] The risk is greatest for patients who have been using high doses of benzodiazepines over an extended period.

[i] Do not coadminister this medication with ritonavir-boosted nirmatrelvir in patients with hepatic or renal impairment.

[j] For medications that are not included on the Liverpool COVID-19 Drug Interactions website or in the University of Waterloo/University of Toronto drug interaction guide, refer to the FDA labels for information on coadministering these medications with ritonavir or other strong CYP3A4 and/or P-gp inhibitors (e.g., ketoconazole).

[k] Dexamethasone exposure is expected to increase 2.60-fold when dexamethasone is coadministered with ritonavir-boosted nirmatrelvir.[5] Clinicians should weigh the risks and benefits of continuing the patient's normal dose of dexamethasone (while monitoring for AEs) against the risks and benefits of decreasing the dose. Patients who are receiving higher doses of dexamethasone will be at a greater risk of AEs.

[l] Patients should take ritonavir-boosted nirmatrelvir at least 3 hours after taking brincidofovir.

[m] Ritonavir-boosted nirmatrelvir interacts with certain conjugated mAbs, such as ado-trastuzumab emtansine, mirvetuximab soravtansine, brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated mAbs, refer to the drug's FDA prescribing information and consult the patient's specialist providers as needed.

Key: AE = adverse effect; ARV = antiretroviral; BPH = benign prostatic hyperplasia; CHA_2DS_2-VASc = congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; CYP = cytochrome P450; FDA = Food and Drug Administration; LMWH = low-molecular-weight heparin; mAb = monoclonal antibody; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase 5; P-gp = P-glycoprotein; PO = oral

Drug-Drug Interaction Considerations When Using Extended Courses of Ritonavir-Boosted Nirmatrelvir (Paxlovid)

The guidance in this document is based on the drug-drug interaction potential of the FDA-approved, 5-day course of ritonavir-boosted nirmatrelvir. Longer treatment courses may be utilized in certain cases (see Special Considerations in People Who Are Immunocompromised). Clinicians should be aware that the drug-drug interaction potential of ritonavir may change based on the duration of treatment. Clinicians should also be aware that:

- Induction properties[6] may become clinically relevant when ritonavir is used for longer durations (i.e., ≥10 days) or chronically (e.g., in people who take HIV protease inhibitors).[7] For example, induction of CYP2C9 and CYP2C19 may decrease warfarin and voriconazole concentrations, and induction of glucuronidation may decrease lamotrigine or valproic acid concentrations.
- The management strategies listed in Box 2 are based on the drug-drug interaction potential of a 5-day treatment course of ritonavir-boosted nirmatrelvir. These strategies may need to be modified when using extended courses. For example, a clinician may need to withhold or reduce the dose of a corticosteroid instead of continuing it as suggested in Box 2. Clinicians may need to adjust monitoring plans for adverse effects or therapeutic drug monitoring in certain patients (e.g., in those receiving tacrolimus). In other cases, the potential risks of withholding certain agents (e.g., chemotherapeutic agents or statins in high-risk individuals) for extended periods to allow for safe coadministration of ritonavir-boosted nirmatrelvir may outweigh the potential benefits of treatment.
- After longer courses of ritonavir-boosted nirmatrelvir are discontinued, drug-drug interactions caused by CYP3A4 inhibition are expected to resolve within 2 to 3 days.[2] Drug-drug interactions caused by induction (e.g., CYP2C9, CYP2C19, UGT) resolve gradually and variably.[8,9]

Clinicians should consult with experts (e.g., pharmacists and physicians with HIV expertise) when using extended courses of ritonavir-boosted nirmatrelvir. The Liverpool COVID-19 Drug Interactions website also provides guidance for managing drug-drug interactions during extended courses (i.e., ≥10 days) of ritonavir-boosted nirmatrelvir.

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