



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

Last Updated: September 26, 2022

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

This is not a comprehensive list of all the medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.^a

Medications Without Clinically Relevant Interactions			
These medications may be coadministered without dose adjustment and without increased monitoring. ^a This list is not inclusive of all noninteracting medications within each drug category.			
<p>Acid reducers</p> <ul style="list-style-type: none"> • Famotidine • Omeprazole • Pantoprazole <p>Allergy</p> <ul style="list-style-type: none"> • Cetirizine • Diphenhydramine • Fexofenadine • Loratadine <p>Anti-infectives</p> <ul style="list-style-type: none"> • Azithromycin • Cidofovir • Hydroxychloroquine • Tecovirimat • Valacyclovir <p>Cardiovascular</p> <ul style="list-style-type: none"> • Aspirin • Atenolol • Carvedilol • Furosemide • Hydrochlorothiazide • Irbesartan • Isosorbide dinitrate • Lisinopril 	<p>Cardiovascular, continued</p> <ul style="list-style-type: none"> • Losartan • Metoprolol • Prasugrel <p>Diabetes</p> <ul style="list-style-type: none"> • Empagliflozin • Insulin • Metformin • Pioglitazone <p>Immunosuppressants</p> <ul style="list-style-type: none"> • Abrocitinib • Baricitinib • Methotrexate • Mycophenolate • Prednisone <p>Lipid-modifiers</p> <ul style="list-style-type: none"> • Ezetimibe • Pitavastatin • Pravastatin <p>Migraine</p> <ul style="list-style-type: none"> • Frovatriptan • Naratriptan • Rizatriptan • Sumatriptan 	<p>Neuropsychiatric</p> <ul style="list-style-type: none"> • Amitriptyline • Bupropion • Citalopram • Duloxetine • Escitalopram • Fluoxetine • Gabapentin • Lorazepam • Nortriptyline • Olanzapine • Paroxetine • Sertraline • Venlafaxine <p>Pain</p> <ul style="list-style-type: none"> • Acetaminophen • Aspirin • Codeine • Ibuprofen • Meloxicam • Naproxen 	<p>Respiratory</p> <ul style="list-style-type: none"> • Corticosteroids (inhaled) • Formoterol • Montelukast <p>Miscellaneous</p> <ul style="list-style-type: none"> • Allopurinol • Contraceptives (oral)^b • Cyclobenzaprine • Donepezil • Enoxaparin • Finasteride • Levothyroxine • Most monoclonal antibody products^c • Ondansetron

Medications Without Clinically Relevant Interactions, continued

^a 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 July 31, 2022 (internal communication, August 2022).

^b The FDA EUA 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 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 oral contraceptive.

^c Ritonavir-boosted nirmatrelvir interacts with certain conjugated monoclonal antibodies, such as those conjugated to the drug monomethyl auristatin E (or vedotin). These include brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated monoclonal antibodies, refer to the drug's FDA prescribing information and consult with the patient's specialist providers as needed.

Key: EUA = Emergency Use Authorization; FDA = Food and Drug Administration

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 adults of advanced age.¹

Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized by the current Food and Drug Administration (FDA) Emergency Use Authorization (EUA), and there are insufficient data on the efficacy of administering a second treatment course in cases where SARS-CoV-2 viral rebound is suspected. The guidance in this document is based on the drug-drug interaction potential of the FDA-authorized 5-day course of ritonavir-boosted nirmatrelvir.

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 select outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.
 - Box 2 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](https://www.liverpoolcovid19.org/)

- Tables with guidance on managing specific drug-drug interactions:
 - The [Ontario COVID-19 Science Advisory Table](#)
 - The FDA EUA [fact sheet](#) and [checklist](#) for ritonavir-boosted nirmatrelvir

Consider consulting with an expert (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 drug-drug interaction when choosing management strategies for patients who will be receiving ritonavir-boosted nirmatrelvir. Potential strategies include:

- Increasing monitoring for potential adverse reactions 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 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 adult of advanced age or if the interacting medication has a long half-life.

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)

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 <ul style="list-style-type: none"> • Carbamazepine • Phenobarbital • Phenytoin • Primidone Anti-infectives <ul style="list-style-type: none"> • Glecaprevir/pibrentasvir • Rifampin • Rifapentine 	Immunosuppressants <ul style="list-style-type: none"> • Voclosporin Cardiovascular <ul style="list-style-type: none"> • Amiodarone • Clopidogrel^{a,b} • Disopyramide • Dofetilide • Dronedarone • Eplerenone • Flecainide 	Cardiovascular, continued <ul style="list-style-type: none"> • Ivabradine • Propafenone • Quinidine Neuropsychiatric <ul style="list-style-type: none"> • Clozapine • Lurasidone • Midazolam (oral) • Pimozide 	Pulmonary hypertension <ul style="list-style-type: none"> • Sildenafil • Tadalafil • Vardenafil Miscellaneous <ul style="list-style-type: none"> • Bosentan • Certain chemotherapeutic agents^c • 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 an adult of advanced age or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

<p>Anticoagulants</p> <ul style="list-style-type: none"> • Rivaroxaban^d <p>Anti-infectives</p> <ul style="list-style-type: none"> • Erythromycin <p>BPH</p> <ul style="list-style-type: none"> • Alfuzosin • Silodosin <p>Cardiovascular</p> <ul style="list-style-type: none"> • Aliskiren • Ranolazine • Ticagrelor^b • Vorapaxar 	<p>Immunosuppressants^e</p> <ul style="list-style-type: none"> • Everolimus • Sirolimus • Tacrolimus <p>Lipid-modifiers</p> <ul style="list-style-type: none"> • Atorvastatin^f • Lomitapide • Lovastatin^f • Rosuvastatin^f • Simvastatin^f <p>Migraine</p> <ul style="list-style-type: none"> • Eletriptan • Rimegepant • Ubrogepant 	<p>Neuropsychiatric</p> <ul style="list-style-type: none"> • Suvorexant • Triazolam^g <p>Erectile dysfunction</p> <ul style="list-style-type: none"> • Avanafil <p>Respiratory</p> <ul style="list-style-type: none"> • Salmeterol <p>Miscellaneous</p> <ul style="list-style-type: none"> • Certain chemotherapeutic agents^c • Colchicine^h • Finerenone • Flibanserin • 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.ⁱ 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>Anticoagulants</p> <ul style="list-style-type: none"> • Apixaban • Dabigatran • Edoxaban <p>Anti-infectives</p> <ul style="list-style-type: none"> • Clarithromycin • Itraconazole • Ketoconazole • Maraviroc • Rifabutin <p>BPH</p> <ul style="list-style-type: none"> • Tamsulosin <p>Cardiovascular</p> <ul style="list-style-type: none"> • Cilostazol • Digoxin • Mexiletine <p>Diabetes</p> <ul style="list-style-type: none"> • Saxagliptin 	<p>Erectile dysfunction</p> <ul style="list-style-type: none"> • Sildenafil • Tadalafil • Vardenafil <p>Immunosuppressants</p> <ul style="list-style-type: none"> • Cyclosporine^e • Dexamethasoneⁱ • Fedratinib • Ruxolitinib • Tofacitinib • Upadacitinib <p>Migraine</p> <ul style="list-style-type: none"> • Almotriptan^h <p>Neuropsychiatric</p> <ul style="list-style-type: none"> • Alprazolam^g • Aripiprazole • Brexpiprazole • Buspirone • Cariprazine • Chlordiazepoxide^g • Clobazam^g • Clonazepam^g • Clorazepate^g 	<p>Neuropsychiatric, continued</p> <ul style="list-style-type: none"> • Diazepam^g • Estazolam^g • Flurazepam^g • Iloperidone • Lumateperone • Pimavanserin • Quetiapine • Trazodone <p>Pain</p> <ul style="list-style-type: none"> • Fentanyl • Hydrocodone • Oxycodone <p>Pulmonary hypertension</p> <ul style="list-style-type: none"> • Riociguat <p>Miscellaneous</p> <ul style="list-style-type: none"> • Certain chemotherapeutic agents^c • Darifenacin • Elexacaftor/tezacaftor/ivacaftor • Eluxadoline • Ivacaftor • Solifenacin • Tezacaftor/ivacaftor
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Continue Concomitant Medication and Monitor for Adverse Effects

Pre-emptive dose adjustment is not required but may be considered based on an individualized assessment of the patient's risk for adverse reactions. Educate patients about 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 as needed.ⁱ

<p>Anticoagulants</p> <ul style="list-style-type: none"> • Warfarin <p>Anti-infectives</p> <ul style="list-style-type: none"> • Brincidofovir^k • Cobicistat- or ritonavir-boosted antiretrovirals • Isavuconazole • Posaconazole • Voriconazole <p>BPH</p> <ul style="list-style-type: none"> • Doxazosin • Terazosin 	<p>Diabetes</p> <ul style="list-style-type: none"> • Glyburide <p>Cardiovascular</p> <ul style="list-style-type: none"> • Amlodipine • Diltiazem • Felodipine • Nifedipine • Sacubitril • Valsartan • Verapamil <p>Migraine</p> <ul style="list-style-type: none"> • Zolmitriptan 	<p>Neuropsychiatric</p> <ul style="list-style-type: none"> • Haloperidol • Hydroxyzine • Mirtazapine • Risperidone • Ziprasidone • Zolpidem <p>Pain</p> <ul style="list-style-type: none"> • Buprenorphine • Hydromorphone • Methadone • Morphine • Tramadol 	<p>Miscellaneous</p> <ul style="list-style-type: none"> • Certain chemotherapeutic agents^c • Certain conjugated monoclonal antibodies^l • Oxybutynin
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^a Reduced effectiveness of clopidogrel is likely. It may be acceptable to continue clopidogrel if the benefits of using ritonavir-boosted nirmatrelvir outweigh the risk of reduced clopidogrel effectiveness.

^b For patients at 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 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 fact sheet 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.

^d For patients who are at high risk of arterial or venous thrombosis (e.g., those who 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 such as LMWH or an alternative COVID-19 therapy. For patients with a lower risk for arterial or venous thrombosis, clinicians may consider administering low-dose aspirin while rivaroxaban is being withheld.

^e 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, is not feasible. Consult a patient's specialist providers before coadministering these immunosuppressants and ritonavir-boosted nirmatrelvir. See the [American Society of Transplantation statement](#) for more information.

^f 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 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.

^g The guidance on managing drug-drug interactions between certain benzodiazepines and ritonavir-boosted nirmatrelvir can vary significantly between resources. The guidance in this table is based on the FDA EUA fact sheet for ritonavir-boosted nirmatrelvir. Note that 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.

^h For patients with hepatic or renal impairment, do not coadminister this medication with ritonavir-boosted nirmatrelvir.

ⁱ For medications that are not included on the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table, refer to the FDA labels for information on coadministering these medications with ritonavir or other strong CYP3A4 and/or P-gp inhibitors.

Continue Concomitant Medication and Monitor for Adverse Effects, continued

^j Dexamethasone exposure is expected to increase 2.60-fold when dexamethasone is coadministered with ritonavir-boosted nirmatrelvir.³ Clinicians should weigh the risks and benefits of continuing the patient's normal dose of dexamethasone (while monitoring for AEs) versus decreasing the dose. Patients who are receiving higher doses of dexamethasone will be at a greater risk of AEs.

^k Patients should take ritonavir-boosted nirmatrelvir at least 3 hours after receipt of brincidofovir.

^l Ritonavir-boosted nirmatrelvir interacts with certain conjugated monoclonal antibodies, such as those conjugated to the drug monomethyl auristatin E (or vedotin). These include brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated monoclonal antibodies, refer to the drug's FDA prescribing information and consult with the patient's specialist providers as needed.

Key: AE = adverse effect; 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; LMWH = low-molecular-weight heparin; P-gp = P-glycoprotein

References

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3. Li M, Zhu L, Chen L, Li N, Qi F. Assessment of drug-drug interactions between voriconazole and glucocorticoids. *J Chemother.* 2018;30(5):296-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30843777>.