

The COVID-19 Treatment Guidelines Panel’s Statement on Potential Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

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On December 22, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for ritonavir-boosted nirmatrelvir (Paxlovid) for the treatment of patients with mild to moderate COVID-19 who are within 5 days of symptom onset and at high risk of progression to severe disease.^{1,2} The dose for patients with normal renal function is nirmatrelvir 300 mg (two 150 mg tablets) plus ritonavir 100 mg (one 100 mg tablet) orally twice daily for 5 days. For more information, see the COVID-19 Treatment Guidelines Panel’s (the Panel) [statement on treatment options for nonhospitalized patients with mild to moderate COVID-19](#).

Ritonavir-boosted nirmatrelvir (Paxlovid) has significant and complex drug-drug interaction potential, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong cytochrome P450 (CYP) 3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. Ritonavir is an FDA-approved drug that has been used for more than 2 decades as a pharmacologic boosting agent for certain anti-HIV medications; therefore, there is a large body of literature describing its use with other drugs and its potential for serious and sometimes life-threatening drug-drug interactions. **Clinicians who are not experienced in prescribing ritonavir-boosted drugs should refer to resources such as the [EUA fact sheet for ritonavir-boosted nirmatrelvir \(Paxlovid\)](#) and the [Liverpool COVID-19 Drug Interactions website](#) for additional guidance.** Consultation with an expert (e.g., clinical pharmacist, HIV specialist, and/or the patient’s specialist provider[s], if applicable) should also be considered.

Ritonavir is an inhibitor, inducer, and substrate of various drug-metabolizing enzymes and/or drug transporters. Most notably, as a strong inhibitor of CYP3A, it may increase concentrations of certain concomitant medications, thereby increasing the potential for significant drug toxicities. CYP3A inhibition by ritonavir typically resolves 3 to 5 days after the drug is discontinued. When ritonavir is used for a treatment duration of 5 days, its induction properties are less likely to be clinically relevant than when the drug is used chronically for HIV. In addition, both nirmatrelvir and ritonavir are substrates of CYP3A; thus, administration of this treatment with or immediately after discontinuing medications that are strong inducers of CYP3A4 (e.g., rifampin) can lead to significant reductions in nirmatrelvir and ritonavir concentrations, which may decrease nirmatrelvir’s effectiveness against SARS-CoV-2.

Assess for Potential Drug-Drug Interactions

- **Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid), clinicians should carefully review concomitant medications, including over-the-counter medicines and herbal supplements, to evaluate the potential for drug-drug interactions.**
- The [EUA fact sheet for ritonavir-boosted nirmatrelvir \(Paxlovid\)](#) and the [Liverpool COVID-19 Drug Interactions website](#) are useful for identifying and managing drug-drug interactions.
- Drug classes of particular concern are those that include drugs that are prone to concentration-dependent toxicities, including (but not limited to) certain antiarrhythmics, oral anticoagulants, immunosuppressants, anticonvulsants, antineoplastics, and neuropsychiatric drugs.
- If a significant drug-drug interaction is identified, clinicians should consider the risks and benefits of using ritonavir-boosted nirmatrelvir (Paxlovid). Expert consultation (e.g., with a clinical pharmacist, HIV specialist, and/or the patient’s specialist provider[s], if applicable) should be considered, especially for patients receiving highly specialized therapies, such as antineoplastics,

neuropsychiatric drugs, and certain immunosuppressants.

- Potential management strategies to facilitate the use of ritonavir-boosted nirmatrelvir (Paxlovid) may differ depending on the magnitude and significance of the interaction. Potential strategies include:
 - Dose adjustment of the concomitant medication
 - Use of an alternative to the concomitant medication
 - Increased monitoring for potential adverse reactions to the concomitant medication
 - In some instances, temporary withholding of the concomitant medication
- The dose of ritonavir-boosted nirmatrelvir (Paxlovid) should not be adjusted to avoid or mitigate a drug-drug interaction with a concomitant medication.
- Patients should be informed of ritonavir-boosted nirmatrelvir's (Paxlovid) drug-drug interaction potential. If a drug-drug interaction is identified, the patient should be informed and advised of the signs and symptoms of potential adverse effects.
- These strategies should be considered for the 5-day duration of ritonavir-boosted nirmatrelvir (Paxlovid) treatment and for at least 3 to 5 days after treatment completion, and for potentially longer if ritonavir-boosted nirmatrelvir (Paxlovid) is administered with an interacting concomitant medication that has a long half-life.
- In settings where these management strategies are not feasible or where the effectiveness of ritonavir-boosted nirmatrelvir (Paxlovid) may be compromised, consider using alternative COVID-19 therapies (see the [Panel's statement on treatment options for nonhospitalized patients with mild to moderate COVID-19](#) for more information).
- The EUA for ritonavir-boosted nirmatrelvir (Paxlovid) suggests that individuals who use products containing ethinyl estradiol for contraception should use a backup, nonhormonal contraceptive method because ritonavir-boosted nirmatrelvir (Paxlovid) has the potential to decrease ethinyl estradiol levels. However, the enzyme-inducing effects of ritonavir-boosted nirmatrelvir (Paxlovid) that would lead to lower hormone exposure are not expected to be clinically significant during 5 days of therapy and, therefore, would not be expected to decrease contraceptive effectiveness. In addition, ethinyl estradiol is always combined with a progestin for contraception. Progestin concentrations are expected to remain similar or increase when ritonavir-boosted nirmatrelvir (Paxlovid) is used concomitantly with combined hormonal contraception, which maintains the effectiveness of the oral contraceptive.

Medications That Are Contraindicated or Should Not Be Coadministered With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

This table is a guide and **not a comprehensive list of all possible drugs that may interact or should not be coadministered with ritonavir-boosted nirmatrelvir (Paxlovid). For example, many drugs that may require dose adjustment or increased monitoring when coadministered with ritonavir-boosted nirmatrelvir (Paxlovid) are not listed in this table.** The [EUA fact sheet for ritonavir-boosted nirmatrelvir \(Paxlovid\)](#) and the [Liverpool COVID-19 Drug Interactions website](#) should be used to identify and manage drug-drug interactions. Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid) for patients receiving highly specialized drugs, such as antineoplastics, consultation with the appropriate specialist providers is recommended.

Deviation from these recommendations may be appropriate in certain clinical scenarios. Providers should exercise clinical judgment when assessing the risks and benefits of ritonavir-boosted nirmatrelvir (Paxlovid) and determine the most appropriate strategy for managing drug-drug interactions

between ritonavir-boosted nirmatrelvir (Paxlovid) and concomitant medications. This is particularly important in the outpatient setting, where close monitoring may not be feasible. Expert consultation should be considered.

In situations where drug-drug interaction risks cannot be mitigated or where the effectiveness of ritonavir-boosted nirmatrelvir (Paxlovid) may be compromised, consider using alternative COVID-19 therapies (see the [Panel’s statement on treatment options for nonhospitalized patients with mild to moderate COVID-19](#) for more information).

<p>Prescribe an alternative COVID-19 therapy for patients who are receiving any of the medications listed.</p>	<p>Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid), determine whether the patient is receiving any of the medications listed.</p> <ul style="list-style-type: none"> • If the patient is receiving any of these medications, withhold the medication if clinically appropriate. • If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.^a
<ul style="list-style-type: none"> • Amiodarone • Apalutamide • Bosentan • Carbamazepine • Cisapride • Clopidogrel • Clozapine • Colchicine in patients with renal and/or hepatic impairment • Disopyramide • Dofetilide • Dronedarone • Eplerenone • Ergot derivatives • Flecainide • Flibanserin • Glecaprevir/pibrentasvir • Ivabradine • Lumateperone • Lurasidone • Mexiletine • Phenobarbital • Phenytoin • Pimozide • Propafenone • Quinidine • Ranolazine • Rifampin • Rifapentine • Rivaroxaban • Sildenafil for pulmonary hypertension • St. John’s wort • Tadalafil for pulmonary hypertension • Ticagrelor • Vorapaxar 	<ul style="list-style-type: none"> • Alfuzosin • Alprazolam • Atorvastatin • Avanafil • Clonazepam • Codeine • Cyclosporine^b • Diazepam • Everolimus^b • Fentanyl • Hydrocodone • Lomitapide • Lovastatin • Meperidine (pethidine) • Midazolam (oral) • Oxycodone • Piroxicam • Propoxyphene • Rosuvastatin • Salmeterol • Sildenafil for erectile dysfunction • Silodosin • Simvastatin • Sirolimus^b • Suvorexant • Tacrolimus^b • Tadalafil for erectile dysfunction • Tamsulosin • Tramadol • Triazolam • Vardenafil

^a Expert consultation may be considered. In some cases, dose reduction of the concomitant medication may be an appropriate management strategy.

^b Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid) for a patient receiving this immunosuppressant, the patient's specialist provider(s) should be consulted, given the significant drug-drug interaction potential between ritonavir and the narrow therapeutic index agent and because close monitoring may not be feasible.

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References

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2. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for paxlovid. 2021. Available at: <https://www.fda.gov/media/155050/download>.