UAB MEDICINE
The University of Alabama at Birmingham

Paxlovid® (nirmatrelvir/ritonavir): Guidance for Drug Interaction Management

I. Background

a. The Food and Drug Administration issued Emergency Use Authorization of Pfizer, Inc.'s Paxlovid® (nirmatrelvir co-packaged with ritonavir) for the treatment of mild to moderate COVID-19 in outpatients with a high risk of progression to severe illness (including hospitalization or death).
b. Paxlovid® is dispensed as nirmatrelvir 150 mg tablets co-packaged with ritonavir 100 mg tablets as a 5-day course of treatment.
c. Ritonavir has multiple effects on the drug metabolism and transport of a variety of medications, which may lead to potentially serious and/or life-threatening adverse reactions.
d. Ritonavir-based enzymatic inhibition may lead to increased serum drug levels with enzymatic activity being restored after 2 to 5 days in certain patients.
e. Guidance for the management of ritonavir-based drug-drug interactions with commonly used medications is provided in the following table.
f. **This is not an all-inclusive list of potential drug interactions with Paxlovid®.** If a drug is not listed below, it cannot be assumed to be safe to co-administer. For any medication not addressed below, please visit http://covid19-druginteractions.org, a reliable source for Paxlovid® drug-drug interactions.
g. Consider contacting a pharmacist for assistance with management of interactions.

DISCLAIMER: These guidelines are intended to support the clinical decision making process and goals of patient care. They should not be used as a substitute for clinical judgement or assessment of individual patient needs.

II. Drug Interaction Management

Medication Name	Effect on Drug Concentration	Recommendation
Alprazolam	↑ Alprazolam levels and risk of toxicity	Consider reducing the dose of alprazolam for patients taking Paxlovid®, monitor for adverse effects such as sedation and respiratory depression.
Antiarrhythmics (amiodarone, dronedarone, flecainide, propafenone, quinidine)	↑ Antiarrhythmic levels and risk of toxicity	**Do not co-administer**; consider an alternative COVID-19 treatment.
Apixaban	↑ Apixaban levels and risk of toxicity	Consider a 50% dose reduction in apixaban for patients taking Paxlovid® who are also at a high risk of thromboembolism. Consider holding apixaban during Paxlovid® treatment and resuming 72 hours after treatment in the following patients:

Apixaban (continued)		(1) Patients with atrial fibrillation (2) Patients taking apixaban at a dose of 2.5 mg (3) Patients with a high risk of bleeding
Aripiprazole	↑ Aripiprazole levels and risk of toxicity	Consider reducing dose of aripiprazole by 50% while taking Paxlovid® and for 3 days after treatment.
Buproprion	↓ Bupropion levels (clinically insignificant)	No dose adjustment needed.
Buspirone	↑ Buspirone levels and risk of toxicity	Hold buspirone while taking Paxlovid® and resume 3 days after treatment. If cannot be held, consider limiting dose of buspirone to 2.5 mg per day.
Calcium channel blockers (amlodipine, diltiazem, felodipine, nicardipine, nifedipine)	↑ Calcium channel blocker levels and risk of toxicity	Closely monitor blood pressure; if hypotension occurs, reduce calcium channel blocker dose by 50% while taking Paxlovid® and for 3 days after treatment.
Carbamazepime	↓ Nirmatrelvir levels and loss of antiviral efficacy	**Do not co-administer**; consider an alternative COVID-19 treatment.
Clozapine	↑ Clozapine levels and risk of toxicity	**Do not co-administer**; consider an alternative COVID-19 treatment.
Clopidogrel	↓ Clopidogrel levels	*Patients with very high-risk of thrombosis (e.g., within 6 weeks of coronary stenting):* **Do not co-administer**; consider an alternative COVID-19 treatment Patients with *low risk of thrombosis*: No dosage adjustments or therapy modifications required.
Colchicine	↑ Colchicine levels and risk of toxicity	Hold colchicine while taking Paxlovid®, and resume 3 days after treatment.

Corticosteroids	No drug-drug interactions expected	No dose adjustment needed.
Cyclosporine	↑ Cyclosporine levels and risk of toxicity	Reduce cyclosporine dose by 75% while taking Paxlovid®; resume previous dose of cyclosporine 3 days after treatment as indicated based on therapeutic drug level monitoring.
Diazepam	↑ Diazepam levels and risk of toxicity	**Do not co-administer**; consider an alternative COVID-19 treatment.
Digoxin	↑ Digoxin levels and risk of toxicity	Reduce digoxin dose by 30-50% while taking Paxlovid® and for 3 days after treatment; may consider therapeutic drug level monitoring. The management of this drug interaction will require individualized dose adjustments based on treatment indication and renal function.
Elbasvir/grazoprevir (Zepatier®)	↑ Grazoprevir levels and risk of hepatotoxicity	**Do not co-administer**; consider an alternative COVID-19 treatment.
Enoxaparin	No drug-drug interactions expected	No dose adjustment needed.
Ethinyl estradiol	↓ Ethinyl estradiol levels	An additional, non-hormonal method of contraception (e.g., barrier methods) should be considered during the 5 days of Paxlovid® and until one menstrual cycle after stopping Paxlovid®.
Estradiol	No drug-drug interactions expected	No dose adjustment needed.
Everolimus	↑ Everolimus levels and risk of toxicity	Hold everolimus while taking Paxlovid®, and resume 3 days after treatment. Adjust dosing based on therapeutic drug level monitoring as indicated.
Fluconazole	No drug-drug interactions expected	No dose adjustment needed.

Fluticasone/ Salmeterol (Advair Disksus®)	↑ Salmeterol levels and risk of cardiac toxicity	Hold salmeterol while taking Paxlovid®, and resume 3 days after treatment. If cannot be held, **do not co-administer**; consider an alternative COVID-19 treatment.
Glecaprevir/ Pibrentasvir (Mavyret®)	↑ Glecaprevir levels and risk of hepatoxicity	**Do not co-administer**; consider an alternative COVID-19 treatment.
Isavuconazole	↑ Isavuconazole levels and risk of toxicity	Monitor for adverse effects such as nausea, diarrhea, abdominal pain, and headache.
Itraconazole	↑ Itraconazole levels and risk of toxicity	Hold itraconazole while taking Paxlovid®, and resume 3 days after treatment. If cannot be held, consider limiting dose of itraconazole to 200 mg per day.
Ketoconazole	↑ Ketoconazole levels and risk of toxicity	Hold ketoconazole while taking Paxlovid®, and resume 3 days after treatment. If cannot be held, consider limiting dose to ketoconazole 200 mg per day.
Levothyroxine	No drug-drug interactions expected	No dose adjustment needed.
Lorazepam	No drug-drug interactions expected	No dose adjustment needed.
Lurasidone	↑ Lurasidone levels and risk of toxicity	**Do not co-administer**; consider an alternative COVID-19 treatment.
Maraviroc	↑ Maraviroc levels and risk of toxicity	Reduce maraviroc dose based on renal function while on Paxlovid® and for 3 days after treatment: • CrCl 30-80 mL/min: 150 mg twice daily • CrCl < 30 mL/min or hemodialysis: **Do not co-administer**; consider an alternative COVID-19 treatment.

Opioids (fentanyl, hydrocodone, oxycodone)	↑ Opioid levels and risk of toxicity	*Fentanyl, hydrocodone, oxycodone:* Reduce opioid dose by 50% while on Paxlovid®. Monitor for signs of respiratory depression.
Opioids (burprenorphine, hydromorphone, methadone, morphine, tramadol)	↓ Opioid levels leading to risk of withdrawal	*Buprenorphine, hydromorphone, methadone, morphine, tramadol*: No dose adjustments are necessary. Monitor for symptoms of withdrawal or decreased efficacy (hydromorphone, methadone) or for toxicity and respiratory depression (buprenorphine).
Phenobarbital	↓ Nirmatrelvir levels and loss of antiviral efficacy	**Do not co-administer**; consider an alternative COVID-19 treatment.
Phenytoin	↓ Nirmatrelvir levels and loss of antiviral efficacy	**Do not co-administer**; consider an alternative COVID-19 treatment.
Quetiapine	↑ Quetiapine levels and risk of toxicity	Consider reducing dose of quetiapine or holding quetiapine until 3 days after the last dose of Paxlovid®.
Rifampin	↓ Nirmatrelvir levels and loss of antiviral efficacy	**Do not co-administer**; consider an alternative COVID-19 treatment.
Rivaroxaban	↑ Rivaroxaban levels and risk of toxicity	**Do not co-administer**; consider an alternative COVID-19 treatment.
Sildenafil	↑ Sildenafil levels and risk of toxicity	*Patients taking sildenafil for pulmonary hypertension:* **Do not co-administer**; consider an alternative COVID-19 treatment. *Patients taking sildenafil for erectile dysfunction:* Consider holding sildenafil during Paxlovid® treatment and resuming 3 days after treatment.

Sirolimus	↑ Sirolimus levels and risk of toxicity	Hold sirolimus while taking Paxlovid®, and resume 3 days after treatment. Adjust dosing based on therapeutic drug level monitoring as indicated.
Sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi®)	↑ Voxilaprevir levels and risk of hepatoxicity	Coadministration has not been studied. Risk of hepatotoxicity is likely minimal with the short course of Paxlovid®. Monitoring of liver function during the course can be considered.
St. John's wort	↓ Nirmatrelvir levels and loss of antiviral efficacy	**Do not co-administer**; consider an alternative COVID-19 treatment.
Statins (atorvastatin, rosuvastatin, lovastatin, simvastatin)	↑ Statin levels and risk of toxicity (variable based on specific agent)	Hold statin at least 12 hours prior to initiation of Paxlovid®. Atorvastatin and rosuvastatin may be resumed 3 days after completing Paxlovid®. Lovastatin and simvastatin may be resumed 5 days after completing Paxlovid®.
Tacrolimus	↑ Tacrolimus levels and risk of toxicity	Hold tacrolimus while taking Paxlovid® and assess tacrolimus concentrations at end of therapy to guide further dosing. Consider obtaining a tacrolimus level on day 3 to assess the need for a one-time tacrolimus dose during Paxlovid® treatment in high-immunologic risk patients. Adjust dosing based on therapeutic drug level monitoring as indicated. If therapeutic drug monitoring is not feasible, consider an alternative COVID-19 treatment.
Tadalafil	↑ Tadalafil levels and risk of toxicity	*Patients taking tadalafil for pulmonary hypertension:* **Do not co-administer**; consider an alternative COVID-19 treatment. *Patients taking tadalafil for erectile dysfunction:* Consider holding tadalafil during Paxlovid® treatment and resuming 3 days after treatment.

Tamsulosin	↑ Tamsulosin levels and risk of hypotension and/or orthostasis	Dose-dependent reduction recommended: (1) Tamsulosin 0.4 mg: No change (monitor blood pressure) (2) Tamsulosin 0.8 mg: Consider holding or decreasing to 0.4 mg
Tenofovir	↑ Tenofovir levels (clinically insignificant)	No dose adjustment needed.
Testosterone	No drug-drug interactions expected	No dose adjustment needed.
Ticagrelor	↑ Ticagrelor levels and risk of toxicity	**Do not co-administer**; consider an alternative COVID-19 treatment.
Trazodone	↑ Trazodone levels and risk of toxicity	Hold trazodone or consider reducing trazodone dose by 50% while taking Paxlovid® and for 3 days after treatment.
Voriconazole	↑↓ Voriconazole levels and risk of toxicity and/or decreased efficacy (concomitant inhibition and induction of metabolism)	Hold voriconazole while taking Paxlovid® and resume 3 days after treatment. Adjust dose based on therapeutic drug level monitoring 5 to 7 days after resumption of voriconazole. If voriconazole cannot be held, consider therapeutic drug level monitoring or close monitoring for adverse effects or lack of treatment efficacy while taking Paxlovid®.
Warfarin	↓ Warfarin levels and decreased therapeutic anticoagulation (i.e., decreased international normalized ratio [INR])	Increase frequency of INR monitoring with co-administration of Paxlovid®. Adjust warfarin dosing as indicated after Paxlovid® treatment.

III. References

1. Lange NW, Salerno DM, Jennings DL, et al. Nirmatrelvir/ritonavir use: managing clinically significant drug-drug interactions with transplant immunosuppressants. doi:10.111/AJT.16955
2. Liverpool COVID-19 Interactions. University of Liverpool. Accessed September 27, 2022. www.covid-19druginteractions.org/checker
3. Lexicomp® Drug Interactions – UpToDate. Accessed September 27, 2022. www.uptodate.com/drug-interactions/

4. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed September 27, 2022.

Contributing Authors:
Kristofer Gutierrez, PharmD[1]; Nicole Hall, PharmD[1]; Joshua Banbury, PharmD[1]; Taylor Sparkman, PharmD[1]; Jeremey Walker, MD[2]; Anoma Nellore, MD[2]; Matthew Brown, PharmD[1]; Seth Edwards, PharmD[1]; Song Ong, MD[2]; Clifton Kew, MD[2]; Robert Cannon, MD[3]; Vineeta Kumar, MD[2].

Affiliations:
[1]Department of Pharmacy, University of Alabama at Birmingham Hospital, Birmingham, AL, United States
[2]Department of Medicine, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States
[3]Department of Surgery, Heersink School of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States

Updated: 12/02/2022