Paxlovid Drug-Interaction Management

· Paxlovid (nirmatrelvir and ritonavir) is a combination antiviral agent that has been shown to significantly reduce the risk of hospitalization or death from COVID in high-risk adults when administered within 5 days of symptom onset.

· Nirmatrelvir blocks the activity of the SARS-CoV-2-3CL protease and is co-administered with ritonavir to slow its metabolism to increase concentrations in the body.

· Ritonavir is a strong CYP3A4 and p-glycoprotein *inhibitor*, a weak CYP2D6 inhibitor, and a moderate *inducer* of CYP2B6, CYP2C19, and CYP2C9 so many off-target drug-drug interactions are possible. Full CYP3A4 inhibition takes place ~ day 2 of ritonavir and can take 2-3 days after ritonavir cessation.

· Dosing: Paxlovid is administered at a dose of 300 mg (two 150 mg tablets) of nirmatrelvir with one 100 mg tablet of ritonavir given twice daily for five days. In patients with renal impairment (GFR 31-60 ml/min), administer a reduced dose of 150 mg of nirmatrelvir with one 100 mg tablet of ritonavir given twice daily for five days. Patients will need to be counseled to only take ONE of the two pink nirmatrelvir tablets for each dose. Use not recommended in patients with severe renal (GFR < 30 mL/min) or hepatic impairment.

· The table below provides recommendations for management of drug-drug interactions for patients being prescribed Paxlovid. Of note, this is not a comprehensive table, but focuses on the most important interactions. Additional information available in Fact Sheet for Healthcare Providers or Liverpool COVID-19 Drug Interaction site. Consider consulting with a pharmacist for specific drug-drug interaction scenarios.

· Many clinically significant interactions with ritonavir may not need to be addressed given the short course of therapy (e.g., inhaled corticosteroids, certain statins).

Management of drug-drug interactions for patients receiving Paxlovid for 5 days

Concomitant Medication	Effect on Ritonavir or Concomitant Medication	Dosing Recommendations and Comments
Antimicrobials		
Rifabutin	Rifabutin AUC ↑ >200%	Adjust dose of rifabutin to 150 mg once daily
Rifampin	Decreased concentrations of Paxlovid expected	Contraindicated
Voriconazole	↓ voriconazole AUC	Use caution, no action needed given short course, consider voriconazole concentration monitoring if turnaround time allows
Antiretrovirals and HCV Therapy		
● Patients on ritonavir- or cobicistat- containing HIV or HCV regimens should continue their treatment as indicated ● Contact provider prior to treatment		

Anticoagulants		
Apixaban	↑ apixaban expected	Consider holding apixaban in patients who require 2.5 mg twice daily In patients requiring apixaban 5 mg or 10 mg twice daily, reduce apixaban dose by 50%
Dabigatran	Modest increase in dabigatran concentrations expected	No change needed. Consider holding in patients with CrCL <50 mL/min
Rivaroxaban	↑ rivaroxaban expected	Hold rivaroxaban. If not feasible to hold, consider every other day dosing during Paxlovid treatment
Warfarin	↓ warfarin possible	Monitor INR closely, induction effects are slow onset and may not be fully appreciated given the short course of therapy
Antiepileptics		
Carbamazepine	↑ carbamazepine Substantial ↓ of Paxlovid expected	Contraindicated
Phenobarbital Phenytoin	Substantial ↓ of phenobarbital and phenytoin expected Substantial ↓ of Paxlovid expected	Contraindicated
Cardiac Medications		
Amiodarone	↑ amiodarone possible ↑ Paxlovid possible	Administer 50% of amiodarone dose, or consider holding altogether given amiodarone's long half-life
Antiarrhythmics (e.g., **dofetilide**, flecainide, mexiletine, propfenone)	↑ antiarrhythmic possible	Contraindicated
Antiplatelets (e.g., ticagrelor, clopidogrel)	↑ ticagrelor possible ↓ clopidogrel active metabolite	Ticagrelor: Contraindicated (if discontinuing ticagrelor cannot be safely done, consider cutting the ticagrelor dose in half) Clopidogrel: For most patients, continuing the same dose is reasonable. For high risk patients, consider administering a "double dose" (i.e., 150 mg)
Digoxin	↑ digoxin concentrations expected	Empirically dose reduce digoxin by 50%, or consider holding altogether during Paxlovid treatment
Statins	↑ statin concentrations expected	Atorvastatin and rosuvastatin concentrations are increased anywhere

		from 2- to 5-fold when co-administered with ritonavir (particularly atorvastatin). It's reasonable to temporarily hold (or half) these medications during Paxlovid treatment (although the short duration of Paxlovid is unlikely to cause significant statin-associated toxicities). Simvastatin and lovastatin are considered contraindicated and should be held during the course of Paxlovid treatment.
Calcium Channel Blockers	↑ concentrations expected	Concentrations of nifedipine, amlodipine, diltiazem, and verapamil are increased roughly 2-fold. Consider halving the dose, or temporarily holding them.
Chemotherapy		
• For cytotoxic chemotherapy, consideration should be made to HOLD chemotherapy until COVID infection resolves • For non-cytotoxic chemotherapy, and/or if consideration is being made to continue chemotherapy, TigerConnect "UMMC Clinical Pharmacist – Outpatient Oncology" (7am-5pm, 7 days/week) to assess for possible drug-drug interactions.		
Hormone Therapies		
Estrogen containing contraceptives	↓ Ethinyl estradiol possible	Use back-up, non-hormonal method of contraception
Immunosuppressants		
Cyclosporine, sirolimus, tacrolimus, everolimus	↑ immunosuppressant expected	Hold during treatment. Resume pre-treatment dose 24-48 hours after last Paxlovid dose. Check trough level 5-7 days after resuming.
PAH Medications		
PDE5 Inhibitors (avanafil, sildenafil, tadalafil, vardenafil)	↑↑↑ PDE5 AUCs expected	Contraindicated
Other **Contraindicated** Medications		
● Alfuzosin ● Analgesics: Meperidine, piroxicam ● Antipsychotic agents: clozapine, lurasidone, pimozide ● Colchicine ● Dihydroergotamine, ergotamine, methylergonovine	● Oral Midazolam ● Ranolazine ● St John's Wort ● Triazolam	
Other Precautions		
● Methadone - ritonavir can decrease concentrations of methadone, monitor patients closely for evidence of withdrawal ● Quetiapine - consider empirically reducing quetiapine dose by 50%		