Appendix A: Paxlovid Drug Interactions – Modified from NIH Table[1]

Tier 1) Prescribe an alternative COVID-19 therapy for patients who are receiving any of the medications listed.	
Antiarrhythmics	Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, ivabridine, mexiletine, propafenone, quinidine
Antianginal	Ranolazine (if used as an antiarrhythmic)

Anticoagulants (indication: VTE)	Prescribe an alternative COVID-19 therapy. If alternative therapy NOT possible then:
	
	Apixaban/rivaroxaban for VTE Treatment (<u>for A.fib/VTE prophylaxis in high risk patients, see Tier 2</u>)
	• **Apixaban – if on 5 mg BID**:
	  ○ Reduce apixaban to 2.5 mg BID (while on Paxlovid + 3 days after = 8 days total) and monitor
	• **Apixaban – if on 2.5 mg BID**
	  ○ Restart Paxlovid 12 hours after last dose of apixaban
	  ○ Hold apixaban and substitute with *enoxaparin* 1 mg/kg every 12 hours **<u>(wait 12 hours after last dose of apixaban to start enoxaparin)</u>**
	  ○ Enoxaparin x 8 days (5 days while on Paxlovid + 3 days after last dose of Paxlovid)
	  ○ **Day 9:** stop enoxaparin and restart apixaban at the time of the next scheduled dose of enoxaparin. **<u>DO NOT ADMINSTER ENOXAPARIN</u>**.
	• **Rivaroxaban:**
	  ○ Wait to start Paxlovid 24 hours after the last dose of rivaroxaban
	  ○ Hold rivaroxaban and substitute with enoxaparin **<u>(wait 24 hours after last dose of rivaroxaban to start enoxaparin)</u>**
	  ▪ Enoxaparin 1 mg/kg every 12 hours x 8 days (5 days while on Paxlovid + 3 days after last dose of Paxlovid)
	  ○ **Day 9:** stop enoxaparin and restart rivaroxaban at the time of the next scheduled dose of enoxaparin. **<u>DO NOT ADMINSTER ENOXAPARIN.</u>**

Anti-epileptics	Carbamazepine, phenobarbital/primidone, phenytoin
Antimicrobials	Rifampin, rifapentine
Antiplatelet	Clopidogrel (if within 6 weeks of stenting), ticagrelor, vorapaxar
Antipsychotics	Lurasidone, pimozide, clozapine, lumateperone
Benzodiazepines	Midazolam (oral), triazolam
CFTR modulators (indication: CF)	Orkambi (lumacaftor/ivacaftor)
Ergot derivatives	Dihydroergotamine, ergotamine, methylergonovine
Gout	Colchicine (if taking daily for gout prevention and pt has severe hepatic/renal impairment)
Hepatitis C antivirals	Glecaprevir/pibrentasvir
Immunosuppressants	Cyclosporine, everolimus, sirolimus, tacrolimus, voclosporin
Multikinase inhibitors	**Recommend discussing with heme-onc provider and MAB team for holding or interrupting therapy while on Paxlovid** • Acalabrutinib, bosutinib, cobimetinib, ibrutinib, pazopanib, regorafenib
Opioids	Fentanyl, meperidine
PDE5 Inhibitors (indication: PH)	Sildenafil, tadalafil, vardenafil
Pulmonary HTN	Bosentan, macitentan
Miscellaneous	Apalutamide, flibanserin, ivabradine, lomitapide, tolvaptan, riociguat, St. John's Wort

Tier 2) If the patient is receiving any of these medications, **hold or dose adjust the concomitant medication if clinically appropriate (see individual agents for specific instructions)**. If withholding is not clinically appropriate, use an alternative COVID-19 therapy.

Generally, ritonavir inhibitory effects are no longer present three days after final dose but can be prolonged in elderly and renally impaired pts. Agents with wide therapeutic index/low risk of severe outcome **can be held for 8 days** from first Paxlovid dose, narrow therapeutic **index/high toxicity risk agents may need to be held for 10 days**.

Aldosterone antagonists/ K+-sparing diuretics	Eplerenone – Recommend discussing with provider for holding or alternative therapy while on Paxlovid
Antiarrhythmic	Digoxin – dose can be reduced by 30-50% with monitoring x 8 days
Anticoagulants (indication: atrial fibrillation)	**Apixaban/rivaroxaban for Atrial fibrillation** • Rivaroxaban: can hold x 10 days • Apixaban: reduce to 2.5 mg BID x 8 days (5 days of Paxlovid + 3 days after last dose of Paxlovid) o If patient is already on apixaban 2.5 mg BID, can continue on case-by-case basis **Apixaban/rivaroxaban for VTE prophylaxis in high risk patients:** • Recommend discussing with provider or pharmacist for holding or enoxaparin as alternative therapy while on Paxlovid
Alpha-1 Antagonists	Alfuzosin, sildosin – can hold x 8 days Tamsulosin – can hold x 8 days or consider using tamsulosin 0.4 mg/day or every other day **(MAX 0.4 mg/day tamsulosin if coadministered with Paxlovid)**

Antimigraine	**CGRP Antagonists**
	• Ubrogepant, rimegepant – hold x 8 days
	Triptans
	• Almotriptan – use 6.25 mg and do not exceed 12.5 mg within 24 hr x 8 days
	• Zolmitriptan – max 5 mg per day x 8 days
	• Eletriptan
	  o Recommend discussing with provider for holding or alternative therapy while on Paxlovid
	  o Sumatriptan, zolmitriptan, and frovatriptan may be acceptable alternatives to eletriptan

Antiplatelet	Clopidogrel – discuss risk of diminished platelet inhibition with provider Cilostazol – reduce dose to 50 mg BID x 8 days
Antipsychotics	Aripiprazole – dose can be reduced by 50% with monitoring x 8 days *(*dose reduction not recommended when used as adjunctive therapy for major depressive disorder)* Brexpiprazole – dose can be reduced by 50% with monitoring x 8 days Quetiapine – dose can be reduce to one-sixth of original dose with monitoring x 8 days
Benzodiazepines	Alprazolam – dose can be reduced by 50% with monitoring x 8 days Clonazepam, diazepam – Can hold x 8 days or use with caution • Recommend discussing with provider or pharmacist if lorazepam can be substituted for clonazepam or diazepam if needed.
Calcium Channel Blockers	Amlodipine, felodipine, nifedipine – dose can be reduced by 50% x 8 days Diltiazem, verapamil – use with caution or dose can be reduced by 50% (or dose every other day if ER formulation) if needed x 8 days
Contraceptives (oral combination)	Consider backup non-hormonal contraceptive NOTE: The EUA for ritonavir-boosted nirmatrelvir suggests that individuals who use products containing ethinyl estradiol for contraception should use a backup, non-hormonal contraceptive method because ritonavir-boosted nirmatrelvir has the potential to decrease ethinyl estradiol levels. However, the enzyme-inducing effects are not expected to be clinically significant during 5 days of therapy and would not be expected to decrease contraceptive effectiveness. In addition, ethinyl estradiol is combined with a progestin and exposure would be unchanged or increase with ritonavir which maintains the effectiveness of the oral contraceptive.

CFTR modulators (indication: CF)	**Kalydeco:** • Day 1: take 1 tablet (150 mg) in AM • Day 2-4: do not take Kalydeco • Day 5: take 1 tablet (150 mg) in AM • Day 6-8: do not take Kalydeco • Day 9: resume Kalydeco 150 mg PO BID **Symdeko:** • Day 1: take 1 yellow tablet in AM and skip the light blue (ivacaftor) tablet in PM • Day 2-4: do not take Symdeko • Day 5: take 1 yellow tablet in AM and skip the light blue (ivacaftor) tablet in PM • Day 6-8: do not take Symdeko • Day 9: resume normal Symdeko regimen (1 tablet in AM and 1 tablet in PM) **Trikafta:** • Day 1: take 2 light orange tablets in AM and skip the light blue (ivacaftor) tablet in PM • Day 2-4: do not take Trikafta • Day 5: take 2 light orange tablets in AM and skip the light blue (ivacaftor) tablet in PM • Day 6-8: do not take Trikafta • Day 9: resume normal Trikafta regimen (2 tablets in AM and 1 tablet in PM)
Gout	Colchicine • if taking PRN and no severe hepatic/renal impairment – Can hold x 10 days • if taking daily for gout prevention and no severe hepatic/renal impairment): ○ Recommend discussing with provider for holding or alternative therapy while on Paxlovid
JAK inhibitors	**Recommend discussing with heme-onc provider or rheumatologist and MAB team for holding or dose reduction of therapy while on Paxlovid** • Fedratinib – reduce dose to 200 mg per day x 8 days then 300 mg per day x 2 weeks then increase to 400 mg per day • Ruxolitinib – reduce dose by 50% x 8 days • Tofacitinib – reduce total daily dose by 50% x 8 days • Upadacitinib – max 15 mg per day x 8 days
Long-acting beta agonists (inhaled)	Salmeterol (Brand names: Serevent, Wixela; Component of Advair Diskus) – Can hold x 8 days; Can consider temporary substitution with non-salmeterol LABA (e.g. formoterol-based [Dulera, Symbicort])
Multikinase inhibitors	**Recommend discussing with heme-onc provider and MAB team for holding or dose reduction of therapy while on Paxlovid** • Afatinib, axitinib, cabozantinib, ceritinib, crizotinib, dabrafenib, dasatinib, erlotinib, lapatinib, nilotinib, ponatinib, sunitinib, vemurafenib
Opioids	Codeine, meperidine, tramadol – Can hold x 10 days • Codeine and tramadol (if co-administration is necessary): consider discussing with provider or pharmacist for alternative therapy while on Paxlovid Oxycodone – dose can be decreased by 75% with monitoring Hydrocodone – dose can be decreased by 50% with monitoring
PDE5 Inhibitors	Avanafil, sildenafil, tadalafil, vardenafil – Can hold x 8 days if used for erectile dysfunction
Statins	Atorvastatin – can hold x 8 days • If co-administration of atorvastatin is necessary, **<u>reduce to atorvastatin 10 mg daily</u>** and resume the usual dose 3 days after completing Paxlovid) Lovastatin, rosuvastatin, simvastatin – can hold x 8 days
Miscellaneous	Buspirone – dose can be reduced to max 2.5 mg daily with monitoring x 8 day Saxagliptin – reduce dose to 2.5 mg daily x 8 days Solifenacin – reduce dose to 5 mg daily x 8 days Trazodone – consider dose reduction with monitoring x 8 days Warfarin – careful monitoring of INR • Consider checking INR on day 3 of Paxlovid and 3 days after Paxlovid