Appendix 1[1]: Examples of Major Drug-Drug Interactions with Nirmatrelvir-ritonavir and Co-administration Advice*

Interacting drug class	Example medication(s)	Type of interaction	Co-administration advice/mitigation strategy
Antiarrhythmics	Amiodarone, Dronedarone	Increased toxicity (CYP3A4 inhibition)	CANNOT BE MITIGATED Do not co-administer due to risk of serious life-threatening arrhythmias. Amiodarone has a long half-life: stopping will not overcome this interaction.
	Digoxin	Increased toxicity (P-gp inhibition)	THERAPEUTIC DRUG MONITORING Measure a digoxin level after 48-72 hours of co-administration and monitor for signs of toxicity; consider reducing dose by 50% during co-administration
Oral antithrombotic agents**	Rivaroxaban	Increased toxicity (P-gp and CYP3A4 inhibition)	DO NOT CO-ADMINISTER Very high increased risk of bleeding
	Apixaban	Increased toxicity (P-gp and CYP3A4 inhibition)	HOLD, REDUCE DOSE or DO NOT CO-ADMINISTER Some product monographs suggest co-administration is possible if the thrombotic risk is low and apixaban dose can be reduced to 2.5 mg po BID[1] High increased risk of bleeding
	Edoxaban	Increased toxicity (P-gp inhibition)	REDUCE DOSE and MONITOR CLINICALLY Co-administration possible. If the thrombotic risk is low, consider a dose reduction to 30 mg po once daily Moderate increased risk of bleeding

	Dabigatran	Possible toxicity (Mixed P-gp inhibition and induction)	MONITOR CLINICALLY Co-administration possible. Monitor clinically for signs of bleeding. Increased risk of bleeding possible
	Warfarin	Increased toxicity (CYP3A4 inhibition)	THERAPEUTIC DRUG MONITORING Measure INR after 48-72 hours of co-administration and adjust dose; repeat INR 48-72 hours following completion of therapy Moderate increased risk of bleeding
	Ticagrelor	Increased toxicity (CYP3A4 inhibition)	DO NOT CO-ADMINISTER Do not co-administer due to high increased risk of bleeding. If the indication for ticagrelor is remote (e.g., >3-6months) holding the drug may be an option Prasugrel can potentially be used as an alternative treatment
Anticonvulsants	Carbamazepine or Phenytoin	Reduced efficacy of nirmatrelvir-ritonavir (CYP3A4 induction by carbamazepine and phenytoin)	CANNOT BE MITIGATED Do not co-administer. Potential development of virological resistance. Use an alternative treatment for COVID-19
Neuropsychiatric drugs	Quetiapine	Increased toxicity (CYP3A4 inhibition)	DO NOT CO-ADMINISTER Hold quetiapine if low dose (12.5-50mg daily) used for sleep or agitation For higher doses prescribed for a psychiatric condition, consult psychiatry and pharmacy. High risk of sedation
Benzodiazepines	Diazepam Midazolam	Increased toxicity (CYP3A4 inhibition)	DO NOT CO-ADMINISTER Risk of extreme sedation and respiratory depression.

			Temporarily holding chronic, regular use benzodiazepines is not advisable as this can precipitate seizures in the absence of tapering.
Opioids	Fentanyl	Increased toxicity (CYP3A4 inhibition)	DO NOT CO-ADMINISTER Fatal respiratory depression can occur Temporarily holding chronic, regular use opioids is not advisable as this can precipitate withdrawal in the absence of tapering.
	Methadone	Reduced effect (CYP3A4 induction)	CLINICAL MONITORING A preemptive dose increase is not needed but should be considered in patients reporting symptoms of withdrawal
Immunosuppressants	Tacrolimus	Increased toxicity (CYP3A4 and P-gp substrate)	PHARMACIST CONSULTATION STRONGLY ADVISED Substantial risk for rapid onset tacrolimus toxicity. Some experts suggest this is not easily mitigated even with substantial dose reductions and routine monitoring of levels. Consider use of an alternative treatment for COVID-19
Alpha1 -Adrenoreceptor Antagonist	Alfuzosin, Tamsulosin	Increased toxicity (CYP3A4 inhibition)	DO NOT CO-ADMINSTER Hold alfuzosin or tamsulosin during and for 3-5 days post treatment. Risk of significant hypotension
Other	Rifampin	Reduced efficacy of nirmatrelvir-ritonavir (CYP3A4 induction by rifampin)	DO NOT CO-ADMINISTER Potential for treatment failure and development of virological resistance.

	Ethinyl estradiol containing hormonal contraception	May reduce efficacy of hormone-based contraceptives (Increased metabolism)	USE A BACK-UP Non-hormonal method of contraception is recommended until the following cycle
	Simvastatin, Atorvastatin, Lovastatin	Risk of rhabdomyolysis or myopathy (CYP3A4 inhibition)	DO NOT CO-ADMINSTER Discontinue statin at least 12 hours prior to nirmatrelvir-ritonavir administration and resume 3-5 days post treatment completion or change to another low-potency statin such as pravastatin
	Colchicine	Increased (fatal) toxicity especially in patients with renal or hepatic failure (CYP3A4 inhibition)	DO NOT CO-ADMINISTER If used for gout, hold colchicine during and for 3-5 days after treatment. If the drug cannot be held (e.g., treatment of familial mediterranean fever) do not use nirmatrelvir-ritonavir. Risk of fatal colchicine toxicity

*__This table is not an exhaustive list of drug-drug interactions__.

One of several free COVID-19 drug interaction guides is available at https://www.covid19-druginteractions.org/checker.

**If holding or reducing the dose of an oral anticoagulant consultation with hematology, cardiology or internal medicine is advised.

We **strongly recommend** pharmacist consultation for patients receiving **concomitant HIV and/or Hepatitis C treatments, active chemotherapy, oral anticoagulants, or are a transplant recipient**. Likewise, if reducing quetiapine or other psychiatric medications prescribed for a psychiatric disorder such as bipolar affective disorder or schizophrenia, consultation with **the patient's mental health practitioner** is advisable.

For all others, expert **consultation** with a pharmacist and shared decision making with any subspecialists is **advisable** whenever possible to
1) Decrease risks of toxicity and 2) Increase the proportion of those eligible for timely treatment.

1 https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf