Updated: June 6, 2022

Nirmatrelvir/ Ritonavir (*Paxlovid™*)

What Prescribers and Pharmacists Need to Know

SCIENCE TABLE
COVID-19 ADVISORY FOR ONTARIO

UNIVERSITY OF WATERLOO | SCHOOL OF PHARMACY

Why is nirmatrelvir/ritonavir used to treat COVID-19?

COVID-19 has an initial phase of viral replication and a significant inflammatory response in moderate illness. This inflammation can lead to poor outcomes, including hospitalization, invasive ventilation, and death. However, treatments that target SARS-CoV-2 replication, if administered before the inflammatory phase of COVID-19, can improve outcomes.

Nirmatrelvir works by binding to the SARS-CoV-2 3CL protease, which ultimately causes viral replication to stop. Ritonavir is a potent CYP3A4 inhibitor. It is not active against SARS-CoV-2 but is administered as a "boosting agent" to slow the metabolism of nirmatrelvir, thus increasing concentrations of nirmatrelvir.

Nirmatrelvir/ritonavir is a highly effective outpatient therapy based on available data, but there is uncertainty about effect magnitude in target populations and high certainty for harm with ritonavir **if drug interactions are not mitigated.**

What is the benefit of nirmatrelvir/ritonavir for COVID-19?

The EPIC-HR study[1] has shown a benefit from treatment of adult outpatients with laboratory-proven SARS-CoV-2 infection who were not on supplemental oxygen and were within 5 days of symptom onset. The study suggests that nirmatrelvir/ritonavir may reduce the risk of hospitalization in these patients by 88%.

Research on nirmatrelvir/ritonavir was done in unvaccinated patients and prior to circulation of the Omicron variant. However, a study suggests that nirmatrelvir/ritonavir retains activity against the Omicron variant in vitro.[2] The Ontario Science Advisory Table recommends the use of nirmatrelvir/ritonavir in COVID-19 patients who are not on supplemental oxygen but are at high risk of progression to moderate or severe COVID-19.[3]

Who should receive nirmatrelvir/ritonavir?

Nirmatrelvir/ritonavir should be offered to patients at **higher risk** of severe COVID-19 *(proven by PCR* or a provider-administered rapid test),* who are not yet on supplemental oxygen, and who are within 5 days of symptom onset.

*PCR = polymerase chain reaction

AGE (years)	NUMBER OF VACCINE DOSES			RISK FACTORS
	0 doses	1 or 2 doses	3 doses	
<20[1]	**Higher risk** if ≥3 risk factors[1]	Standard risk[1]	Standard risk[1]	• Obesity (BMI ≥30 kg/m²) • Diabetes • Heart disease, hypertension, congestive heart failure • Chronic respiratory disease, including cystic fibrosis • Cerebral palsy • Intellectual disability • Sickle cell disease • Moderate or severe kidney disease (eGFR <60 mL/min) • Moderate or severe liver disease (e.g., Child Pugh Class B or C cirrhosis)
20 to 39	**Higher risk** if ≥3 risk factors	**Higher risk** if ≥3 risk factors	Standard risk	
40 to 69	**Higher risk** if ≥1 risk factors	**Higher risk** if ≥3 risk factors	Standard risk	
≥70	**Higher risk**	**Higher risk** if ≥1 risk factors	**Higher risk** if ≥3 risk factors	
Immunocompromised[2] individuals of any age	**Higher risk**: Therapeutics should always be recommended for immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying immune status, regardless of age or vaccine status.[1,2]			
Pregnancy	**Higher risk**[3]	Standard risk	Standard risk	

1. Evidence for the safety and efficacy of sotrovimab and nirmatrelvir/ritonavir (Paxlovid) in children <18 years of age is limited. While early evidence on risk factors for moderate and severe COVID-19 in children is emerging, the ability to reliably predict disease progression in children remains very limited, and the frequency of progression is rare. While not routinely recommended in children <18 years of age, the use of these agents may be considered in exceptional circumstances (e.g., severe immunocompromise and/or multiple risk factors, clinical progression) on a case-by-case basis. Multidisciplinary consultation with Infectious Diseases (or Pediatric Infectious Diseases) and the team primarily responsible for the child's care is recommended to review the individual consideration of these medications.
2. Examples of immunocompromised or immunosuppressed individuals include receipt of treatment for solid tumors and hematologic malignancies (including individuals with lymphoid malignancies who are being monitored without active treatment), receipt of solid-organ transplant and taking immunosuppressive therapy, receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy), moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good's syndrome, hyper IgE syndrome), advanced or untreated HIV infection, active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory. These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.
3. Therapeutics should always be recommended for pregnant individuals who have received zero vaccine doses.

From: "Clinical Practice Guideline Summary: Recommended Drugs and Biologics in Adult Patients with COVID-19. (Version 11.0)"
https://covid19-sciencetable.ca/sciencebrief/#infectious-diseases-clinical-care.

Indigenous persons (First Nations, Inuit, or Métis), Black persons, and members of other racialized communities may be at high risk of disease progression due to disparate rates of comorbidity, increased vaccination barriers, and social determinants of health, and should be considered priority populations for access to COVID-19 therapeutics. Nirmatrelvir/ritonavir may be considered in pregnant or lactating patients on an individual basis if the benefits of treatment outweigh the potential risks.

Alice Tseng, PharmD, FCSHP, AAHIVP; Claudia Bucci, BScPhm, PharmD, ACPR; Matthew Chow, BScPhm, PharmD, ACPR; Pierre Giguère, BPharm, MSc AAHIVP; Kelly Grindrod, PharmD; Bassem Hamandi, BScPhm, PhD; Heather Kertland, PharmD, FCSHP; Rosemary Killeen, BScPhm, PGCert, RPh; Todd Koch, BScPhm; Adam S. Komorowski, MD; Sharan Lail, BScPhm, PharmD, ACPR; Kori Leblanc, BScPhm, PharmD, ACPR; Andrew Morris, MD, FRCPC; Menaka Pai, MSc, MD, FRCPC; Christine Papoushek, PharmD; Linda Robinson, BSc.Phm, AAHIVP; Tessa Senneker, PharmD, ACPR; Deborah Yoong, BScPhm, ACPR, PharmD; Beth Leung, PharmD, MSCI, BCPS AQID.
Design: Adrian Poon, BA.

How do I dose nirmatrelvir/ritonavir for treatment of COVID-19?

1. Paxlovid consists of 2 drugs packaged together:
   - Nirmatrelvir (pink) 150 mg tablet
   - Ritonavir (white) 100 mg tablet
2. Each carton contains 5 blister cards. One blister card is used each day. The full course of treatment is 5 days.
3. Take 2 pink tablets of nirmatrelvir and 1 white tablet of ritonavir (3 tablets total) together at the same time, once in the morning and once in the evening for 5 days (i.e., 6 tablets per day).
   - Nirmatrelvir/ritonavir may be taken with or without food.

Special Dosing Considerations:

eGFR† 30 to 59 mL/min:
Nirmatrelvir 150 mg and ritonavir 100 mg taken together orally BID x 5 days.

eGFR† <30 mL/min:[4]
Day 1: Nirmatrelvir 300 mg and ritonavir 100 mg
Days 2-5: Nirmatrelvir 150 mg and ritonavir 100 mg once daily.

Dialysis: Give after dialysis.

If dialysis and weight <40 kg:
Nirmatrelvir 150 mg and ritonavir 100 mg q48h x 3 doses; give after dialysis.

Severe hepatic impairment (Child-Pugh Class C):
Nirmatrelvir/ritonavir is not recommended.

†eGFR = estimated glomerular filtration rate

What side effects should I be aware of?

Common side effects of nirmatrelvir/ritonavir are generally mild and can include dysgeusia (taste disturbance), diarrhea, hypertension, myalgia, vomiting and headache.

Not many people have taken this drug, and it is still being studied - so it is possible that all the side effects are not yet known, or that rare, but serious side effects may happen.

Paxlovid product monograph

Or visit:
https://covid-vaccine.canada.ca/info/pdf/paxlovid-pm-en.pdf

What drug interactions should I consider before prescribing nirmatrelvir/ritonavir?

- **Ritonavir is a potent inhibitor of CYP3A4 isoenzyme and various drug transporters (e.g., P-glycoprotein).**
  - Onset of ritonavir inhibition is rapid and takes a few days to dissipate after completion of therapy.
- **Ritonavir and nirmatrelvir are both CYP3A4 substrates.**
- **Nirmatrelvir/ritonavir is contraindicated in patients taking drugs that are:**
  - Highly metabolized by CYP3A4 where elevated concentrations can be life-threatening.
  - Potent CYP3A4 inducers which may reduce the effectiveness of nirmatrelvir/ritonavir and contribute to the development of drug resistance.

What if my patient is taking therapy for human immunodeficiency virus (HIV)?

Patients taking ritonavir or cobicistat for HIV therapy should continue their complete antiretroviral regimen at usual dosing while taking nirmatrelvir/ritonavir.

What if my patient is taking a drug that interacts with nirmatrelvir/ritonavir?

⚠ If the patient is taking or has taken a **CYP3A4 enzyme inducer** in the last 14 days (e.g., certain anticonvulsants, antineoplastics, a rifamycin, St. John's wort): Do NOT prescribe nirmatrelvir/ritonavir.

▲ If the patient takes an interacting drug with a **long plasma half-life and narrow therapeutic window** (e.g., certain antiarrhythmics, antipsychotics, antineoplastics), the interacting drug will persist in the body after the last dose and may still interact with nirmatrelvir/ritonavir: Do NOT prescribe nirmatrelvir/ritonavir even if the interacting drug can be held.

● If the patient takes an interacting drug that can be held, hold the drug starting the first day of nirmatrelvir/ritonavir therapy, and resume 2 days after the last dose of nirmatrelvir/ritonavir treatment.

◆ A specialist prescriber or pharmacist may be able to help adjust the dose or dosing interval, replace the drug with an alternative agent, manage side effects, and guide therapeutic drug monitoring.

Nirmatrelvir/ritonavir has many drug interactions. See page 3 →

1 Hammond J, Leister-Tebbe H, Gardner A, Abreu P et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *NEJM*. doi: 10.1056/NEJMoa2118542
2 Vangeel L, Chiu W, De Jonghe S, Maes P, et al. Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *Antiviral Res.* 2022;198:105252. doi: 10.1016/j.antiviral.2022.105252.
3 Ontario COVID-19 Science Advisory Table. Clinical Practice Guideline Summary: Recommended Drugs and Biologic in Adult Patients with COVID-19. (Version 11.0). Published April 11, 2022. https://covid19-sciencetable.ca/sciencebrief/#infectious-diseases-clinical-care.
4 Ontario Renal Network. COVID-19 Supplemental Clinical Guidance #4: Nirmatrelvir/Ritonavir (Paxlovid) Use in Patients With Advanced Chronic Kidney Disease and Patients on Dialysis with COVID-19. Published April 13, 2022. https://www.ontariohealth.ca/sites/ontariohealth/files/2022-04/PaxlovidClinicalGuide.pdfv

Nirmatrelvir/Ritonavir (*Paxlovid*) Drug Interactions:

This is not an exhaustive list. Consultation with a pharmacist who can obtain a complete medication, recreational, and natural health product history from the patient is recommended prior to prescribing nirmatrelvir/ritonavir.

Symbol	Severity	Recommendation	Rationale
▲	Contraindicated	Use alternative COVID agent. **Do not use nirmatrelvir/ritonavir.**	Stopping the drug will not mitigate the interaction (e.g., prolonged half-life, narrow therapeutic index, prolonged enzyme-inducing effects which may decrease effectiveness of nirmatrelvir/ritonavir). Do not coadminister due to risk of serious toxicity.
◬	Contraindicated (use within past 14 days)		
●	Do not coadminister	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Significant ↑ in drug concentrations expected. Do not coadminister due to risk of serious toxicity.
◆	Caution	Therapy modification required (see Appendix).	Significant ↑/↓ in drug concentrations expected, which may lead to serious toxicity or impaired efficacy. Only coadminister if the interacting drug can be safely held or dose-adjusted and closely monitored (see Appendix). Expert consultation may be useful.
✔	Drug interaction not likely to be clinically relevant	Continue with standard dosing.	Although mentioned in the monograph, clinically relevant interaction is not anticipated (e.g., minimal impact on certain metabolic pathways, wide therapeutic index, and short course of nirmatrelvir/ritonavir).

- ◆ Abemaciclib (*Verzenio*)
- ● Alfuzosin (*Xatral*)
- ◆ Alprazolam (*Xanax*)
- ▲ Amiodarone
- ✔ Amitriptyline
- ◆ Amlodipine (*Norvasc*)
- ◬ Apalutamide (*Erleada*)
- ◆ Apixaban (*Eliquis*)
- ◆ Aripiprazole (*Abilify*), oral
- ◆ Atorvastatin (*Lipitor*)
- ✔ Atovaquone
- ▲ Bosentan (*Tracleer*)
- ● Bosutinib (*Bosulif*)
- ◆ Brexpiprazole (*Rexulti*)
- ✔ Budesonide
- ✔ Bupropion
- ◆ Buspirone (*Buspar*)
- ◬ Carbamazepine (*Tegretol*)
- ◆ Ceritinib (*Zykadia*)
- ● Cisapride
- ✔ Citalopram
- ✔ Clarithromycin
- ✔ Clomipramine
- ● Clonazepam
- ◆ Clopidogrel (*Plavix*)
- ● Clorazepate
- ▲ Clozapine (*Clozaril*)
- ● Cobimetinib (*Cotellic*)
- ● Colchicine in renal/hepatic impairment
- ◆ Cyclosporine (*Neoral*)
- ◆ Dabigatran
- ◬ Dabrafenib (*Tafinlar*)
- ◆ Dasatinib (*Sprycel*)
- ◆ Dexamethasone, high dose
- ● Diazepam (*Valium*)
- ◆ Digoxin
- ◆ Diltiazem (*Tiazac, Cardizem*)
- ✔ Divalproex
- ● Dofetilide
- ✔ Dronabinol
- ▲ Dronedarone (*Multaq*)
- ◆ Edoxaban (*Lixiana*)
- ◆ Elagolix (*Orilissa*)
- ◆ Encorafenib (*Braftovi*)
- ◬ Enzalutamide
- ● Ergot alkaloids (e.g., dihydroergotamine, ergonovine)
- ◬ Eslicarbazepine
- ✔ Ethinyl estradiol
- ● Everolimus (*Certican*)
- ◆ Felodipine
- ▲ Fentanyl (*Duragesic*)
- ▲ Flecainide
- ✔ Fluoxetine
- ● Flurazepam
- ✔ Fluvoxamine
- ◆ Fostamatinib (*Tavalisse*)
- ✔ Fusidic acid, topical
- ● Glecaprevir/Pibrentasvir (*Maviret*)
- ◆ Hydrocodone
- ● Ibrutinib (*Imbruvica*)
- ✔ Imipramine
- ✔ Itraconazole
- ✔ Ketoconazole
- ✔ Lamotrigine
- ● Lomitapide (*Juxtapid*)
- ◬ Lorlatinib (*Lorbrena*)
- ● Lovastatin
- ▲ Lurasidone (*Latuda*)
- ✔ Maprotiline
- ✔ Maraviroc
- ● Meperidine (*Demerol*)
- ✔ Methamphetamine
- ✔ Metoprolol
- ● Midazolam, oral
- ◬ Mitotane (*Lysodren*)
- ◆ Modafinil
- ● Neratinib (*Nerlynx*)
- ◆ Nifedipine
- ◆ Nilotinib (*Tasigna*)
- ● Nitrazepam (*Mogadon*)
- ✔ Nortriptyline
- ◬ Oxcarbazepine
- ◆ Oxycodone (*Percocet, OxyNEO*)
- ✔ Paroxetine
- ◬ Phenobarbital
- ◬ Phenytoin (*Dilantin*)
- ▲ Pimozide
- ◬ Primidone
- ▲ Propafenone
- ◆ Quetiapine (*Seroquel*)
- ▲ Quinidine
- ● Quinine
- ✔ Raltegravir
- ▲ Ranolazine (*Corzyna*)
- ◆ Rifabutin
- ◬ Rifampin
- ◬ Rifapentine
- ◆ Risperidone (*Risperdal*), oral
- ▲ Risperidone, long-acting injection (*Risperdal Consta*)
- ● Rivaroxaban (*Xarelto*)
- ◆ Rosuvastatin (*Crestor*)
- ● Salmeterol (*Serevent, Advair*)
- ✔ Sertraline
- ◆ Sildenafil for ED† (*Viagra*)
- ▲ Sildenafil for PAH‡ (*Revatio*)
- ● Silodosin (*Rapaflo*)
- ● Simvastatin
- ● Sirolimus (*Rapamune*)
- ▲ Sonidegib (*Odomzo*)
- ◬ St. John's wort (*Hypericum perforatum*)
- ● Tacrolimus (*Prograf, Advagraf, Envarsus*)
- ◆ Tadalafil for ED† (*Cialis*)
- ▲ Tadalafil for PAH‡ (*Adcirca*)
- ● Tamsulosin (*Flomax*)
- ▲ Tepotinib (*Tepmetko*)
- ✔ Theophylline
- ● Ticagrelor (*Brilinta*)
- ✔ Timolol
- ◆ Tramadol
- ● Triazolam (*Halcion*)
- ✔ Trimipramine
- ● Vardenafil (*Levitra*) for ED†
- ▲ Vardenafil (*Levitra*) for PAH‡
- ▲ Venetoclax (*Venclexta*)
- ✔ Venlafaxine
- ◆ Verapamil
- ◆ Vinblastine
- ◆ Vincristine
- ✔ Voriconazole
- ◆ Warfarin
- ◆ Ziprasidone (*Zeldox*)
- ◆ Zolpidem (*Sublinox, Ambien*)
- ◆ Zopiclone (*Imovane*)

Liverpool's COVID-19 Interaction Checker
https://www.covid19-druginteractions.org/

University Health Network & Kingston Health Sciences Centre Paxlovid-Oncology DDI
https://www.antimicrobialstewardship.com/paxlovid-ddi-oncology

†ED = erectile dysfunction ‡PAH = pulmonary arterial hypertension

Appendix: Nirmatrelvir/ritonavir (*Paxlovid*) Drug Interactions

June 6, 2022. This document will be updated as more information becomes available.

Guiding principles for managing drug interactions categorized as 🛑 and 🔶.

There is limited drug interaction data for nirmatrelvir/ritonavir (which is a potent CYP3A4/P-glycoprotein inhibitor). Most potential interactions listed below are based on known/anticipated effects with ritonavir alone or with other protease inhibitors. In some instances, pharmacokinetic interaction data for other potent CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) are included in this table to help predict the potential extent of an interaction effect with nirmatrelvir/ritonavir.

General recommendation: 🛑 🔶

Hold the interacting drug for one week (i.e., beginning on the first day of nirmatrelvir/ritonavir and resuming two days after completing nirmatrelvir/ritonavir).

› *Ritonavir inhibition is not immediately reversible.*

If holding a drug for one week is not a safe option:

- Use an alternative COVID-19 agent for 🛑 drugs, or;
- Consider therapy modification for 🔶 drugs.

Caution: ⚠

Some drugs may need to be held longer due to a greater sensitivity to ritonavir inhibition (e.g., calcineurin inhibitors).

In many instances, replacing a drug is not feasible, and may introduce more risk of harm or error (e.g., patient takes both the held and new drug, forgets to restart original drug, etc).

› Recommendations in this appendix are based on Canadian product monographs, the Liverpool COVID-19 Drug Interactions Database (University of Liverpool, 2022), Lexi-Interact Online Database (Hudson OH, Wolters Kluwer, 2022), and additional references as noted.

Disclaimer

This document is intended for use by experienced clinicians, including prescribers and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Clinicians should always consider the risk/benefit profile for their individual patient, discuss these risks with the patient or caregiver before initiating therapy, and closely monitor for treatment benefit and adverse effects.

Neither the Ontario COVID-19 Science Advisory Table, the University of Waterloo, nor the authors and their respective institutions are responsible for deletions or inaccuracies in information or for claims of injury resulting from any such deletions or inaccuracies. Mention of specific drugs, drug doses, or drug combinations within this document does not constitute endorsement by the Ontario COVID-19 Science Advisory Table, the University of Waterloo, or the authors and their respective institutions.

This document is intended to complement (but is separate from) the Ontario COVID-19 Science Advisory Table Drugs and Biologics Clinical Practice Guidelines.

	Drug	Recommendation	Comments
🔶	Abemaciclib (*Verzenio*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, for patients who have not previously had dose reduction for toxicity, consider a dose reduction to 50 mg once daily with close monitoring for toxicity.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Cyclin-dependent kinase inhibitors are generally held for acute infection. Abemaciclib AUC increased over 3-fold when coadministered with clarithromycin.
🛑	Alfuzosin (*Xatral*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, may consider giving every other day in patients with heightened risk of urinary retention. Monitor for hypotension.	Alfuzosin AUC increased 3-fold when coadministered with ketoconazole 400 mg.
🔶	Alprazolam (*Xanax*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce alprazolam dose by at least 50% and monitor for increased effects.	Alprazolam AUC increased 148% and half-life increased from 13 to 30 hours when coadministered with ritonavir 200 mg x 4 doses.
🔶	Amlodipine (*Norvasc*)	Reduce amlodipine dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Amlodipine AUC increased 2-fold when coadministered with indinavir/ritonavir or paritaprevir/ritonavir.

Appendix (Page 2)

Drug	Recommendation	Comments
◆ Apixaban (*Eliquis*)	If possible, use alternative COVID-19 agent. If not possible, ensure stable renal function, then: **A) If already on low dose (2.5 mg BID) apixaban, continue.** **B) If acute venous thromboembolism (VTE):** ⚠ *Low risk of clot:* Hold apixaban. 12 hours after the last dose of apixaban, start nirmatrelvir/ritonavir AND aspirin 81 mg daily. Finish aspirin 1 day after completing nirmaltrevir/ritonavir. Restart apixaban 2 days after completing nirmatrelvir/ritonavir. ⚠ *High risk of clot:* Hold apixaban. 12 hours after the last dose of apixaban, start nirmatrelvir/ritonavir AND therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as: ◦ **Dalteparin** 200 units/kg daily OR 100 units/kg every 12 hours **if >90 kg;** ◦ **Enoxaparin** 1 mg/kg every 12 hours **(preferred)** OR 1.5 mg/kg once every 24 hours; ◦ **Tinzaparin** 175 anti-Xa units/kg once daily. Finish LMWH 1 day after completing nirmatrelvir/ritonavir. Restart apixaban 2 days after completing nirmatrelvir/ritonavir. **C) If atrial fibrillation:** Decrease apixaban to 2.5 mg BID. Resume usual dose 2 days after completing nirmatrelvir/ritonavir. See *Paxlovid for a Patient on a DOAC* for more details. https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/paxlovid_for_a_patient_on_a_doac.pdf	Canadian monograph states that coadministration with ritonavir is contraindicated. However, US product monograph suggests to decrease 5 mg twice daily dose to 2.5 mg twice daily when combined with strong inhibitors of CYP3A4 and P-glycoprotein. Eliquis (U.S.) Prescribing Information. Accessed February 8, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf Observational data from Italy found a 70 to 490% increase in apixaban levels in combination with *antivirals* containing ritonavir in hospitalized patients. Testa S, Prandoni P, Paoletti O et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. *J Thromb Haemost.* 2020;18:1320–1323. https://doi.org/10.1111/jth.14871 ⚠ **High risk of clot includes:** ◦ Clot within past 6 months ◦ Clot at any time in past when anticoagulation interrupted ◦ Active cancer with clot at any point in cancer journey ◦ Diagnosis of antiphospholipid antibody syndrome
◆ Aripiprazole (*Abilify*), oral	Reduce aripiprazole oral dose by 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor for confusion, restlessness, and sedation.	Aripiprazole AUC increased almost 2-fold when coadministered with ketoconazole. No clinically relevant interaction expected with long-acting injection.
◆ Atorvastatin	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce atorvastatin to 10 mg daily. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Atorvastatin AUC increased almost 6-fold when coadministered with lopinavir/ritonavir 400/100 mg twice daily.
● Bosutinib (*Bosulif*)	Hold bosutinib and start nirmatrelvir/ritonavir 24 hours after the last bosutinib dose. Restart bosutinib 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Bosutinib AUC increased almost 9-fold when coadministered with ketoconazole.
◆ Brexpiprazole (*Rexulti*)	Reduce brexpiprazole dose by 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor for confusion, restlessness, sedation.	Brexpiprazole AUC increased 97% when coadministered with ketoconazole.
◆ Buspirone (*Buspar*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce buspirone dose to 2.5 mg daily if the usual dose is 20 to 30 mg/day.	Buspirone AUC increased 19-fold when coadministered with itraconazole 200 mg/day for 4 days.

AUC = Area under the curve

Appendix (Page 3)

Drug	Recommendation	Comments
◆ Ceritinib (*Zykadia*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing ceritinib dose by 33% and monitor for toxicity.	Canadian monograph recommends to avoid concomitant use. However, US monograph suggests reducing dose by 33%, rounded to nearest 150 mg dosage strength. Zykadia (U.S.) Prescribing Information. Accessed February 8, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205755s016lbl.pdf Decision to hold or dose-adjust ceritinib should be made in conjunction with the patient's oncologist. Ceritinib AUC increased 3-fold when single dose coadministered with ketoconazole.
● Cisapride	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Potential for serious and/or life-threatening adverse effects, including cardiac arrhythmias.
● Clonazepam	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
◆ Clopidogrel (*Plavix*)	**Acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI):** • **If <1 month since ACS:** Use alternative COVID-19 agent. • **If <3 months since ACS or <1 month since PCI (no ACS):** Consider switching clopidogrel to prasugrel (if age <75, weight >60 kg, and no history of stroke/TIA) and resume clopidogrel 2 days after completing nirmatrelvir/ritonavir; • **If >3 months since ACS or >1 month since PCI (no ACS):** Continue clopidogrel with acetylsalicylic acid (ASA) during nirmatrelvir/ritonavir therapy. If not taking ASA, consider switching to prasugrel (if age <75, weight >60 kg, and no history of stroke/TIA) and resume clopidogrel 2 days after completing nirmatrelvir/ritonavir.	Coadministration will decrease the antiplatelet effect of clopidogrel. Clopidogrel active metabolite AUC decreased by 51 to 69% when coadministered with ritonavir.
● Clorazepate	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
● Cobimetinib (*Cotellic*)	Hold cobimetinib and start nirmatrelvir/ritonavir 24 hours after the last cobimetinib dose. Restart cobimetinib 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Cobimetinib AUC increased almost 7-fold when coadministered with ketoconazole.
● Colchicine in renal/ hepatic Impairment	Coadministration is contraindicated in patients with renal and/or hepatic impairment. In patients with <u>normal renal/hepatic function,</u> colchicine may be administered at a lowered dose if practical: • **Treatment of gout flares:** 0.6 mg x 1 dose, then 0.3 mg (½ tablet) 1 hour later. Repeat dose no earlier than 3 days. • **Prevention of gout flares:** **a)** If on 0.6 mg twice daily: decrease to 0.3 mg once daily; **b)** If on 0.3 mg twice daily: decrease to 0.3 mg once every 2 days. • **Treatment of Familial Mediterranean fever:** maximum 0.6 mg (or 0.3 mg twice daily). In all cases, resume usual colchicine dose 2 days after completing nirmatrelvir/ritonavir.	Drug interaction could lead to potentially life-threatening/fatal adverse events.

TIA = Transient ischemic attack

AUC = Area under the curve

Appendix (Page 4)

Drug	Recommendation	Comments
Cyclosporine (*Neoral*)	Reduce cyclosporine total daily dose by 80% and start nirmatrelvir/ritonavir 12 hours after the last cyclosporine dose. Continue at reduced dose throughout nirmatrelvir/ritonavir therapy. Resuming transplant immunotherapy after the last dose of nirmatrelvir/ritonavir should be guided by therapeutic drug monitoring and in conjunction with the patient's transplant provider.	Check cyclosporine concentrations 2 days after the last dose of nirmatrelvir/ritonavir. • **If subtherapeutic:** increase cyclosporine dose. Consider resumption of twice daily dosing. • **If therapeutic:** continue with current cyclosporine dose. • **If supratherapeutic:** reduce or hold current cyclosporine dose. In all cases, repeat cyclosporine level in 2 to 4 days and continue to dose-adjust accordingly.
Dabigatran	If possible, use alternative COVID-19 agent. If not possible, then: **A) If already on low dose (110 mg BID) dabigatran, continue.** **B) If acute venous thromboembolism (VTE):** ⚠ *Low risk of clot:* Hold dabigatran. 12 hours after the last dose of dabigatran, start nirmatrelvir/ritonavir AND aspirin 81 mg daily. Finish aspirin 1 day after completing nirmatrelvir/ritonavir. Restart dabigatran 2 days after completing nirmaltrevir/ritonavir. ⚠ *High risk of clot:* Hold dabigatran. 12 hours after the last dose of dabigatran, start nirmatrelvir/ritonavir AND therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as: ◦ **Dalteparin** 200 units/kg daily OR 100 units/kg every 12 hours **if >90 kg;** ◦ **Enoxaparin** 1 mg/kg every 12 hours **(preferred)** OR 1.5 mg/kg once every 24 hours; ◦ **Tinzaparin** 175 anti-Xa units/kg once daily. Finish LMWH 1 day after completing nirmatrelvir/ritonavir. Restart dabigatran 2 days after completing nirmatrelvir/ritonavir. **C) If atrial fibrillation:** Decrease dabigatran to 110 mg BID *(if eGFR>50 mL/minute)* OR decrease to 75 mg BID *(if eGFR 30-50 mL/minute)*. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Dabigatran AUC increased almost 2-fold when coadministered with nirmatrelvir/ritonavir. ⚠ **High risk of clot includes:** ◦ Clot within past 6 months ◦ Clot at any time in past when anticoagulation interrupted ◦ Active cancer with clot at any point in cancer journey ◦ Diagnosis of antiphospholipid antibody syndrome See *Paxlovid for a Patient on a DOAC* for more details. https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/paxlovid_for_a_patient_on_a_doac.pdf
Dasatinib (*Sprycel*)	**Chronic phase chronic myelogenous leukemia (CML):** Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing dasatinib dose to 20 to 40 mg and monitor for toxicity. **Accelerated or blast phase CML:** Do not coadminister; use alternate COVID-19 therapy.	Decisions to hold or dose-adjust dasatinib should be made in conjunction with the patient's oncologist. Dasatinib AUC increased 5-fold when coadministered with ketoconazole.
Dexamethasone, high dose	**High dose (≥20 mg daily):** Reduce dexamethasone dose by 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. **Low dose (<20 mg daily):** Continue with usual dose during nirmatrelvir/ritonavir.	Dexamethasone AUC increased almost 3-fold when coadministered with voriconazole. Li M, Zhu L, Chen L et al. Assessment of drug-drug interactions between voriconazole and glucocorticoids. *J Chemother*. 2018;30(5):296-303. doi: 10.1080/1120009X.2018.1506693. Potential for risk of dexamethasone toxicity with high doses (≥20 mg daily). Clinically significant interaction is not expected with dexamethasone at low doses, including when used for COVID-19 treatment.

AUC = Area under the curve

Appendix (Page 5)

	Drug	Recommendation	Comments
🔴	Diazepam (*Valium*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
🔶	Digoxin	Reduce digoxin dose by 50% OR hold and restart 2 days after completing nirmatrelvir/ritonavir.	
🔶	Diltiazem (*Tiazac, Cardizem*)	Reduce diltiazem dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor heart rate and blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.
🔴	Dofetilide	If possible, use alternative COVID-19 agent. Alternatively, hold dofetilide and restart 2 days after completing nirmatrelvir/ritonavir.	Dofetilide is metabolized to a small extent through CYP3A4.
🔶	Edoxaban (*Lixiana*)	If possible, use alternative COVID-19 agent. If not possible, ensure stable renal function, then: **A) If already on low dose (30 mg once daily) edoxaban, continue.** **B) If acute venous thromboembolism (VTE):** ⚠ *Low risk of clot:* Hold edoxaban. 24 hours after the last dose of edoxaban, start nirmatrelvir/ritonavir AND aspirin 81 mg daily. Finish aspirin 1 day after completing nirmaltrevir/ritonavir. Restart edoxaban 2 days after completing nirmatrelvir/ritonavir. ⚠ *High risk of clot:* Hold edoxaban. 24 hours after the last dose of edoxaban, start nirmatrelvir/ritonavir AND therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as: ◦ **Dalteparin** 200 units/kg daily OR 100 units/kg every 12 hours **if >90 kg;** ◦ **Enoxaparin** 1 mg/kg every 12 hours **(preferred)** OR 1.5 mg/kg once every 24 hours; ◦ **Tinzaparin** 175 anti-Xa units/kg once daily. Finish LMWH 1 day after completing nirmatrelvir/ritonavir. Restart edoxaban 2 days after completing nirmatrelvir/ritonavir. **C) If atrial fibrillation:** Decrease edoxaban to 30 mg daily. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	No drug interaction data available with protease inhibitors but up to a 2-fold increase in exposure is anticipated. Canadian product monograph recommends caution when using with ritonavir; 30 mg daily dose is recommended with P-glycoprotein inhibitors. ⚠ **High risk of clot includes:** ◦ Clot within past 6 months ◦ Clot at any time in past when anticoagulation interrupted ◦ Active cancer with clot at any point in cancer journey ◦ Diagnosis of antiphospholipid antibody syndrome See *Paxlovid for a Patient on a DOAC* for more details. https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/paxlovid_for_a_patient_on_a_doac.pdf
🔶	Elagolix (*Orilissa*)	Potential for increased elagolix concentrations and possibly decreased nirmatrelvir concentrations. Continue with usual elagolix dose during nirmatrelvir/ritonavir therapy and monitor for elagolix toxicity.	Potential for serious adverse effects, including suicidal ideation and elevation of hepatic transaminases. Elagolix AUC increased over 2-fold when coadministered with ketoconazole 400 mg daily.

AUC = Area under the curve

Appendix (Page 6)

	Drug	Recommendation	Comments
◆	Encorafenib (*Braftovi*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider reducing encorafenib dose as follows and monitoring for toxicity: • If taking 450 mg per day: reduce to 150 mg daily. • If taking 150 to 300 mg per day: reduce dose to 75 mg daily. Resume usual encorafenib dose 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust encorafenib should be made in conjunction with the patient's oncologist. Encorafenib AUC increased 3-fold when coadministered with posaconazole.
●	Ergot alkaloids (e.g., dihydroergotamine, ergonovine)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Potential for serious and/or life threatening adverse effects, including acute ergot toxicity.
●	Everolimus (*Certican*)	Hold everolimus and start nirmatrelvir/ritonavir 12 hours after last everolimus dose. Resuming transplant immunotherapy after the last dose of nirmatrelvir/ritonavir should be guided by therapeutic drug monitoring and in conjunction with the patient's transplant provider.	Check everolimus concentrations 2 days after last dose of nirmatrelvir/ritonavir. • **If therapeutic/sub-therapeutic:** resume everolimus at 25 to 50% baseline dose. Repeat level every 2 to 4 days and adjust dose accordingly. • **If supratherapeutic:** continue to hold everolimus; repeat level in 2 to 4 days to assess resumption.
◆	Felodipine	Reduce felodipine dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.
●	Flurazepam	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
◆	Fostamatinib (*Tavalisse*)	Monitor for toxicity including diarrhea, hypertension, hepatotoxicity, and neutropenia. If significant toxicity occurs, consider interruption of fostamatinib with reintroduction 2 days after completing nirmatrelvir/ritonavir.	Fostamatinib active metabolite AUC increased 102% when coadministered with ketoconazole.
●	Glecaprevir/ Pibrentasvir (*Maviret*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Glecaprevir exposure is increased over 4-fold with ritonavir and is associated with increased risk of alanine aminotransferase (ALT) elevation. In patients who are planning to start Hepatitis C (HCV) treatment, glecaprevir/pibrentasvir treatment should be deferred.
◆	Hydrocodone	Reduce dose by about 50% or switch to equivalent dose of hydromorphone: • Multiply hydrocodone dose by 0.25 to get equivalent hydromorphone dose. • Consider further reducing hydromorphone dose by 25 to 50% to account for cross tolerance. Monitor for signs of opioid toxicity. Resume usual hydrocodone dose 2 days after completing nirmatrelvir/ritonavir.	Hydrocodone is metabolized to active metabolites: hydromorphone and norhydrocodone. Hydrocodone AUC increased by 90% when coadministered with ritonavir/ombitasvir/ paritaprevir combination.

AUC = Area under the curve

Appendix (Page 7)

	Drug	Recommendation	Comments
🔴	Ibrutinib (*Imbruvica*)	Consider alternate COVID-19 therapy. Alternatively, consider holding ibrutinib and starting nirmatrelvir/ritonavir 12 hours after the last ibrutinib dose. Restart ibrutinib 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust ibrutinib should be made in conjunction with the patient's oncologist. **It may be dangerous to interrupt therapy in patients with high volume chronic lymphocytic leukemia or mantle cell lymphoma due to disease flare and/or cytokine release.** Ibrutinib AUC increased 26-fold when coadministered with ketoconazole.
🔴	Lomitapide (*Juxtapid*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Lomitapide AUC increased 27-fold when coadministered with ketoconazole.
🔴	Lovastatin	Stop lovastatin at least 12 hours before starting nirmatrelvir/ritonavir. Restart 5 days after completing nirmatrelvir/ritonavir.	Contraindicated due to potential for severe toxicity including rhabdomyolysis and elevated liver function tests.
🔴	Meperidine (*Demerol*)	Do not coadminister. Switch meperidine to an equivalent dose of hydromorphone: • Multiply meperidine dose by 0.02 to get equivalent hydromorphone dose. • Consider further reducing hydromorphone dose by 25 to 50% to account for cross tolerance. Monitor for signs of opioid toxicity. Resume usual meperidine dose 2 days after completing nirmatrelvir/ritonavir.	Normeperidine AUC increased 50% when coadministered with ritonavir. Higher levels of normeperidine can cause central nervous system excitation and seizures.
🔴	Midazolam, oral	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Coadministration may result in large increases in oral midazolam concentrations with the potential for serious events such as prolonged or increased sedation or respiratory depression.
🔶	Modafinil	No dose adjustment required. Monitor for anxiety and agitation.	Coadministration could potentially increase modafinil exposure due to CYP3A4 inhibition. Modafinil is a moderate inducer of CYP3A4, but a clinically significant effect on nirmetrelvir/ritonavir exposure is unlikely.
🔴	Neratinib (*Nerlynx*)	Hold and start nirmatrelvir/ritonavir 24 hours after the last neratinib dose. Restart neratinib 2 days after completing nirmatrelvir/ritonavir.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Neratinib AUC increased almost 5-fold when coadministered with ketoconazole.
🔶	Nifedipine	Reduce nifedipine dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.
🔶	Nilotinib *(Tasigna)*	**Chronic phase chronic myelogenous leukemia (CML):** Hold nilotinib if possible, restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, consider dose reduction to 400 mg PO daily and monitor for toxicity. **Accelerated or blast phase CML:** Do not coadminister. Consider an alternate COVID-19 therapy.	Decisions to hold or dose-adjust nilotinib should be made in conjunction with the patient's oncologist. Canadian monograph recommends holding if using CYP3A4 inhibitors, or monitoring for QTc if treatment interruption is not possible. A 50% dose reduction is recommended based on expected effect on nilotinib exposures. Deeken JF, Pantanowitz I, Dezube BJ. Targeted therapies to treat non-AIDS-defining cancers in patients with HIV on HAART therapy: treatment considerations. *Curr Opin Oncol* 2009; 21(5): 445-54. doi: 10.1097/CC.0b013e32832f3e04 Nilotinib AUC increased 3-fold when coadministered with ketoconazole.

AUC = Area under the curve

Appendix (Page 8)

	Drug	Recommendation	Comments
🔴	Nitrazepam (*Mogadon*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended.
🔶	Oxycodone (*Percocet, OxyNEO*)	Reduce dose of oxycodone by 66% or switch to equivalent dose of hydromorphone: • Multiply oxycodone dose by 0.3 to get equivalent hydromorphone dose. • Consider further reducing hydromorphone dose by 25 to 50% to account for cross tolerance. Monitor for signs of opioid toxicity. Resume usual oxycodone dose 2 days after completing nirmatrelvir/ritonavir.	Oxycodone half-life increased 2-fold and AUC increased between 3 and 4-fold when coadministered with other potent 3A4 inhibitors (i.e., voriconazole).
🔶	Quetiapine (*Seroquel*)	Reduce to one-sixth of original dose and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor for confusion, dizziness, and sedation.	Quetiapine AUC increased 5 to 8-fold when coadministered with ketoconazole.
🔴	Quinine	**For treatment of leg cramps:** Hold and restart 2 days after completing nirmatrelvir/ritonavir. **For treatment of malaria:** Use an alternative COVID-19 agent.	Quinine AUC increased 4-fold and conversion to active metabolite was markedly inhibited when coadministered with ritonavir 200 mg twice daily.
🔶	Rifabutin	Reduce rifabutin to 150 mg once daily; return to 300 mg once daily 2 days after completing nirmatrelvir/ritonavir.	Canadian monograph recommends 150 mg three times a week, but the dose been found to be too low and contributes to resistance. The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents recommends using rifabutin 150 mg daily when used with a ritonavir-boosted protease inhibitor. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/drug-interactions-between-protease-inhibitors-and-other-drugs?view=full Significant increases in exposures of rifabutin (>3-fold) and metabolite (>40-fold) observed when coadministered with lopinavir/ritonavir 400/100 mg twice daily.
🔶	Risperidone (*Risperdal*), oral	Reduce risperidone dose by 25 to 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor for confusion, extrapyramidal symptoms, and sedation.	Risperidone AUC increased up to 2-fold when coadministered with ketoconazole. Avoid coadministration in patients stabilized on risperidone long-acting injection.
🔴	Rivaroxaban (*Xarelto*)	*Next page*	*Next page*

AUC = Area under the curve

Appendix (Page 9)

Drug	Recommendation	Comments
Rivaroxaban (*Xarelto*)	If possible, use alternative COVID-19 agent. If not possible, then: **A) If acute venous thromboembolism (VTE):** ⚠ *Low risk of clot:* Hold rivaroxaban. 24 hours after the last dose of rivaroxaban, start nirmatrelvir/ritonavir AND aspirin 81 mg daily. Finish aspirin 1 day after completing nirmaltrevir/ritonavir. Restart rivaroxaban 2 days after completing nirmatrelvir/ritonavir. ⚠ *High risk of clot:* Hold rivaroxaban. 24 hours after the last dose of rivaroxaban, start nirmatrelvir/ritonavir AND therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as: ◦ **Dalteparin** 200 units/kg daily OR 100 units/kg every 12 hours **if >90 kg;** ◦ **Enoxaparin** 1 mg/kg every 12 hours **(preferred)** OR 1.5 mg/kg once every 24 hours; ◦ **Tinzaparin** 175 anti-Xa units/kg once daily. Finish LMWH 1 day after completing nirmatrelvir/ritonavir. Restart rivaroxaban 2 days after completing nirmatrelvir/ritonavir. **B) If atrial fibrillation:** Hold rivaroxaban. 24 hours after the last dose of rivaroxaban, start nirmatrelvir/ritonavir AND edoxaban 30 mg daily. Finish edoxaban 1 day after completing nirmatrelvir/ritonavir. Restart rivaroxaban 2 days after completing nirmatrelvir/ritonavir.	Rivaroxaban AUC and Cmax increased by 153% and 55%, respectively, when coadministered with ritonavir 600 mg twice daily in healthy volunteers. Observational data from Italy found a 600 to 3000% increase in rivaroxaban levels in combination with *antivirals* containing ritonavir in hospitalized patients. Testa S, Prandoni P, Paoletti O et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. *J Thromb Haemost.* 2020;18:1320–1323. https://doi.org/10.1111/jth.14871 ⚠ **High risk of clot includes:** ◦ Clot within past 6 months ◦ Clot at any time in past when anticoagulation interrupted ◦ Active cancer with clot at any point in cancer journey ◦ Diagnosis of antiphospholipid antibody syndrome See *Paxlovid for a Patient on a DOAC* for more details. https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/paxlovid_for_a_patient_on_a_doac.pdf
Rosuvastatin	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce to 10 mg daily. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Rosuvastatin AUC increased 2-fold and Cmax increased almost 5-fold when coadministered with lopinavir/ritonavir 400/100 mg twice daily.
Salmeterol (*Serevent, Advair*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Potential for serious and/or life-threatening adverse effects, including cardiac arrhythmias (prolonged QTc).
Sildenafil for erectile dysfunction (*Viagra*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce dose to 25 mg once every 48 hours. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Sildenafil AUC increased 2 to 11-fold when coadministered with protease inhibitors.
Silodosin (*Rapaflo*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Silodosin AUC increased over 3-fold when coadministered with ketoconazole.
Simvastatin	Stop simvastatin at least 12 hours before starting nirmatrelvir/ritonavir. Restart 5 days after completing nirmatrelvir/ritonavir.	Contraindicated due to potential for severe toxicity including rhabdomyolysis and elevated liver function tests.
Sirolimus (*Rapamune*)	Hold sirolimus and start nirmatrelvir/ritonavir 24 to 48 hours after the last sirolimus dose. Resuming transplant immunotherapy after the last dose of nirmatrelvir/ritonavir should be done in conjunction with the patient's transplant provider. Use therapeutic drug monitoring to guide sirolimus dose re-adjustment after completion of nirmatrelvir/ritonavir.	Check sirolimus concentration 2 days after last dose of nirmatrelvir/ritonavir. • **If therapeutic/subtherapeutic:** resume sirolimus at 50% of baseline dose. Repeat level every 7 days and dose-adjust accordingly. • **If supratherapeutic:** continue to hold sirolimus and repeat level in 5 to 7 days to assess resumption.

Cmax = Maximum (or peak) serum concentration
AUC = Area under the curve

Appendix (Page 10)

	Drug	Recommendation	Comments
🔴	Tacrolimus (*Prograf, Advagraf, Envarsus*)	Immediate release (*Prograf*, generics): hold tacrolimus and start nirmatrelvir/ritonavir 12 hours after the last tacrolimus dose. Extended (*Advagraf*) or prolonged (*Envarsus*) release: hold the long acting tacrolimus and start nirmatrelvir/ritonavir 24 hours after the last tacrolimus dose. Resuming transplant immunotherapy after the last dose of nirmatrelvir/ritonavir should be guided by therapeutic drug monitoring and in conjunction with the patient's transplant provider.	For all forms of tacrolimus: check tacrolimus concentrations 2 days after the last dose of nirmatrelvir/ritonavir. • **If therapeutic/subtherapeutic:** resume tacrolimus at 25 to 75% of baseline dose; repeat level every 2 to 4 days and adjust dose accordingly. • **If supratherapeutic:** continue to hold tacrolimus; repeat level in 2 to 4 days to assess resumption.
🟡	Tadalafil for erectile dysfunction (*Cialis*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, reduce the dose to 10 mg once every 72 hours. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Tadalafil AUC increased 124% when coadministered with ritonavir 200 mg twice daily.
🔴	Tamsulosin (*Flomax*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. Alternatively, may consider using 0.4 mg daily or giving every other day in patients with heightened risk of urinary retention. Monitor for hypotension.	Tamsulosin AUC increased almost 3-fold when coadministered with ketoconazole.
🔴	Ticagrelor (*Brilinta*)	**Acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI):** • **If <1 month since ACS:** Suggest alternative COVID-19 agent. • **If <3 months since ACS or <1 month since PCI (no ACS):** Switch to prasugrel (if age <75, weight >60 kg, and no history of stroke/TIA) during nirmatrelvir/ritonavir therapy. • **If >3 months since ACS or >1 month since PCI (no ACS):** Consider temporarily holding ticagrelor (i.e., no switching) during nirmatrelvir/ritonavir therapy and resuming after. If not taking acetylsalicylic acid (ASA), consider switching to prasugrel (if age <70, weight >60 kg, and no history of stroke/TIA) or half-dose of ticagrelor (45 mg twice daily).	Ticagrelor AUC increased 36% when coadministered with a single dose of ritonavir 100 mg.
🟡	Tramadol	Reduce tramadol dose by 50% and monitor for pain relief and opioid toxicity. Resume usual dose 2 days after completing nirmatrelvir/ritonavir.	Inhibition of CYP3A4 may increase tramadol concentrations. Inhibition of CYP2D6 can decrease conversion of tramadol to a more active metabolite, but this is not expected to be significant when coadministered with nirmatrelvir/ritonavir.
🔴	Triazolam (*Halcion*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.	Due to prolonged benzodiazepine half-life, coadministration is not recommended. Triazolam half-life increased from 4 to 50 hours when coadministered with ritonavir 200 mg x 4 doses.
🔴	Vardenafil (*Levitra*) for erectile dysfunction	Hold and restart 2 days after completing nirmatrelvir/ritonavir.	Vardenafil AUC increased 49-fold when coadministered with ritonavir 600 mg twice daily.
🟡	Verapamil	Reduce verapamil dose by 50% or take dose every other day. Restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure. May consider continuing with usual dosing in patients at low risk of bradycardia or hypotension.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.

TIA = Transient ischemic attack

AUC = Area under the curve

Appendix (Page 11)

Drug	Recommendation	Comments
Vinblastine	Vinblastine may be held in the context of acute infection. Restart vinblastine at least 2 days after completing nirmatrelvir/ritonavir. Alternatively, vinblastine may be coadministered with close monitoring for hematologic and neurotoxicity. Some providers may wish to empirically reduce vinblastine dose, especially in patients who have previously experienced or are at high risk for toxicity.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Vinblastine AUC increased almost 2-fold when coadministered with ritonavir. Increased risk of autonomic and peripheral neurotoxicity and neutropenia have been reported with coadministration of ritonavir and vinblastine.
Vincristine	Vincristine may be held in the context of acute infection. Restart vincristine 2 days after completing nirmatrelvir/ritonavir. Alternatively, vincristine may be coadministered with close monitoring for hematologic and neurotoxicity. Some providers may wish to empirically reduce vincristine dose, especially in patients who have previously experienced or are at high risk for toxicity.	Decisions to hold or dose-adjust should be made in conjunction with the patient's oncologist. Increased rates of hematologic toxicity and neuropathy (including autonomic neuropathy) have been reported with coadministration of ritonavir and vincristine.
Warfarin	Monitor for signs of increased bleeding and bruising. Check international normalized ratio (INR) if clinically indicated.	Potential for increased warfarin concentrations when coadministered with nirmatrelvir/ritonavir.
Ziprasidone (*Zeldox*)	No dose adjustment required. Monitor for dizziness, extrapyramidal symptoms, and sedation.	Only one-third of ziprasidone dose is metabolized by CYP450. Ziprasidone AUC increased 35 to 40% when coadministered with ketoconazole.
Zolpidem (*Sublinox, Ambien*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If coadministration required, reduce zolpidem dose by 50%.	Zolpidem AUC increased 70% when coadministered with ketoconazole.
Zopiclone (*Imovane*)	Hold and restart 2 days after completing nirmatrelvir/ritonavir. If coadministration required, reduce zopiclone dose by 50%.	Potential for increased zopiclone exposures when coadministered with nirmatrelvir/ritonavir.

AUC = Area under the curve