Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

*The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an **individualized, patient-centric manner**.*
*This tool is intended to provide guidance and **does not replace** clinical judgement.*

INTRODUCTION

Nirmatrelvir/ritonavir (Paxlovid®) was authorized for use by Health Canada for the treatment of mild-to-moderate COVID-19 in adults with a positive COVID-19 test result, and who are at high risk for progression to severe COVID-19, including hospitalization or death. For eligible patients, the recommended treatment course of nirmatrelvir/ritonavir (Paxlovid®) is 300 mg/100 mg po BID x 5 days.
Nirmatrelvir is a SARS-CoV-2 protease inhibitor that works to disrupt viral replication. Ritonavir acts as a "pharmacokinetic booster" to inhibit nirmatrelvir hepatic metabolism and optimize nirmatrelvir plasma concentrations.
Many clinically significant drug-drug interactions exist with nirmatrelvir/ritonavir (Paxlovid®) through the impact of ritonavir on hepatic cytochrome P450 enzymes.

INTENT OF THE TOOL

The Nirmatrelvir/Ritonavir (Paxlovid®) Drug-Drug Interaction Assessment Tool was developed to identify drug-drug interactions and potential management strategies. The tool is intended for use by non-severe COVID-19 designated prescribers as well as collaborating pharmacists, including those on the COVID-19 Non-severe Therapy Pharmacist Consult Service.
This document does not include an exhaustive list of interactions. If a medication is not listed in the table it cannot be assumed to be safe to co-administer. Consult existing drug-drug interaction resources (e.g. University of Liverpool Drug Interaction Database, Ontario Science Table Drug Interaction Overview, Lexicomp) prior to therapy initiation.

STRUCTURE OF THE TOOL

The Nirmatrelvir/Ritonavir (Paxlovid®) Drug-Drug Interaction Assessment Tool contains:

- medications categorized by color (black, red, amber, green) based on the severity of the drug-drug interaction:

▲ **Do not co-administer, alternate COVID-19 therapy advised.**	⊘ **Do not administer nirmatrelvir/ritonavir , unless feasible to hold, dose adjust, switch, increase the monitoring of interacting co-medication.**	○ **Co-administer with caution. May need to adjust the dose and monitor for adverse events.**	● **Co-administer**

- considerations and evidence to help with rationale: information collected from a variety of resources to help rationalize and support clinical judgement,
- conclusion.

PRESCRIBING CONSIDERATIONS

- Consider potential drug interactions with all medications/therapy regardless of route of administration (e.g. prescription medications, over-the-counter products, sample medications, traditional medicines, taken by mouth, injection, eye drops, inhalers, creams, and nasal sprays).
- Not all medications may be documented in the Nova Scotia Drug Information System (DIS). Medications dispensed by hospital pharmacies in Nova Scotia such as oral and systemic Oncology agents, High-Cost Drug Program medications (e.g. medications used for solid organ and bone marrow transplant, HIV and MS, and clozapine) will not consistently appear on DIS. It is critical to obtain a thorough medication history from patients and caregivers including all medication sources.

POTENTIAL FOR DRUG INTERACTIONS

- Both nirmatrelvir and ritonavir are substrates of CYP3A4 and P-glycoprotein (P-gp).
    - Medications that are potent enzyme inducers can significantly reduce concentrations of nirmatrelvir/ritonavir and negatively impact potential efficacy against COVID-19. It is important to note that enzyme induction only reaches maximum effect after several days and lasts long after the co-administration is completed. Therefore, stopping the interacting drug will not mitigate this effect.[1]
- Ritonavir is a strong inhibitor of CYP3A4 and may increase plasma concentrations of medications that are primarily metabolized by CYP3A4.[2]

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

- Clinically significant drug interactions can occur even though the duration of nirmatrelvir/ritonavir (Paxlovid®) treatment is short (i.e. 5 days) because the onset of ritonavir enzyme inhibition is rapid i.e., maximal inhibition of CYP3A4 is reached approximately 48 hours after starting ritonavir.[3]
- The risk of drug interactions is prolonged because CYP3A4 inhibition lasts for several days after ritonavir is discontinued.[3] If co-medications are paused or the dose is adjusted due an interaction caused by enzyme inhibition, it is recommended to wait **three days** after the last dose of nirmatrelvir/ritonavir (Paxlovid®) to resume usual treatment and dose.[3]
- It is important to note that pausing a co-medication with a long half-life of elimination may not prevent a drug interaction with ritonavir.[3]
- In addition, pausing a medication with a narrow therapeutic index may cause harm related to subtherapeutic levels.[4]

- Ritonavir inhibits CYP2D6 to a lesser extent. Co-administration of CYP2D6 substrates with nirmatrelvir/ritonavir (Paxlovid®) for a 5-day course is unlikely to result in clinically significant interactions.
- Ritonavir is also an inducer of UGT, 1A2, 2C9, 2C19, 2B6. However, co-administration of nirmatrelvir/ritonavir (Paxlovid®) with drugs metabolized by these enzymes is unlikely to result in clinically significant reduction in plasma concentrations due to the short 5-day course of nirmatrelvir/ritonavir (Paxlovid®).

ADDITIONAL CONSIDERATIONS

- Very high levels of inflammation observed in some patients with COVID-19 may also cause inhibition of CYP3A4 and P-glycoprotein therefore potentially increasing the magnitude of interactions.[3]
- Management of drug interactions with nirmatrelvir/ritonavir (Paxlovid®) is complex and may include pausing the administration or adjusting the dose of interacting co-medications.[3]
  - Management of some drug interactions is particularly challenging and may require significant dose reduction and increased monitoring that is pragmatically not feasible. In these cases choose alternate COVID-19 therapy where available.
  - Consider collaborating with a specialist whenever feasible for drug interactions that may impact an underlying medical condition.

RESOURCES

Nirmatrelvir/ritonavir (Paxlovid®) General Resources:

- COVID-19 Non-Severe Therapy Pharmacist Consult Service
- NS Health COVID-19 Medication Recommendations
- Non-severe COVID-19 Treatment Overview
- Firstline early treatment algorithm
- Healthcare Professional Overview
- Patient Information Sheet English
- Patient Information Sheet French
- Eligibility Criteria
- Sotrovimab differential benefit algorithm

Nirmatrelvir/ritonavir (Paxlovid®) Drug Interaction Resources:

- University of Liverpool Drug Interaction Database
- NIH Statement on Drug-Drug Interactions
- Ontario Science Table Drug Interaction Overview
- BC COVID THERAPEUTICS COMMITTEE: Drug-Drug Interactions and Contraindications
- Sharedhealth Manitoba: NIRMATRELVIR and RITONAVIR (PAXLOVID) - Information for Health-Care Providers Summary Information

REFERENCES

1. University of Liverpool Drug Interaction Database. Available from: https://www.covid19-druginteractions.org/checker
2. Product Monograph. Available from: https://www.pfizer.ca/sites/default/files/202201/PAXLOVID_PM_E_259186_17Jan2022.pdf
3. University of Liverpool; Duration of CYP3A4 Inhibition after Stopping Paxlovid®. Available from: jic3t6ks120rpb8ucwi537rgjtwg (liverpool-covid19.s3.eu-west-2.amazonaws.com)
4. Ontario Science Table and University of Waterloo: Nirmatrelvir/Ritonavir (Paxlovid®): What Prescribers and Pharmacists Need to Know. Available from: https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know/

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
⛔	Alfuzosin	Xatral®	Alpha-1 Blockers	Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⭕	Tamsulosin	Flomax®		Increased exposure.	Reduce the dose to 0.4 mg/day. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⭕	Silodosin	Rapaflo®		Increased exposure.	Co-administer with caution. Monitor for potential adverse reactions.
▲	Ranolazine	Ranexa®	Antiarrhythmics/ Anti-anginal	Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Amiodarone	n/a	Antiarrhythmics	Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
⛔	Digoxin	Toloxin®		Increased exposure.	If practical, dose reduce by 50% and resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Otherwise, do not co-administer, alternate COVID-19 therapy advised.
▲	Dronedarone	Multaq®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Flecainide	Tambocor®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Propafenone	Rythmol®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Dofetilide	Tikosyn®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Quinidine	Quin-G®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
Anticoagulants: Thrombosis Canada advises that an individualized, patient-centric approach be taken as there may be several management options (e.g., temporarily stopping the DOAC or considering an alternative to nirmatrelvir/ritonavir (Paxlovid®) treatment). Consider bleeding and thrombosis risk, and indication for anticoagulation.					
▲	Apixaban* (for recent VTE)	Eliquis®	Anticoagulants	Increased exposure.	Recent VTE (within 1 month): Do not co-administer, alternate COVID-19 therapy advised.
○	Apixaban* (for AFib)				Atrial Fibrillation: Consider reducing dose of 5 mg po bid to 2.5 mg po bid.
⊘	Rivaroxaban*	Xarelto®		Increased exposure.	If practical, hold or switch to another agent. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Otherwise, do not co-administer, alternate COVID-19 therapy advised.
▲	Edoxaban* (For recent VTE)	Lixiana®		Increased exposure.	Recent VTE (within the last month): Do not co-administer, alternate COVID-19 therapy advised.
○	Edoxaban* (For AFib)				Atrial fibrillation: Reduce dose of 60 mg to 30 mg. Resume regular dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
○	Warfarin*	Coumadin®		Decreased exposure. Small potential for increased exposure.	Co-administer with caution for patients on stable dose. Monitor for signs of increased bleeding and bruising. If practical, may increase monitoring.
▲	Clopidogrel* (For ACS)	Plavix®	Antiplatelets	Decreased exposure.	ACS < 1 month ago or PCI with stents < 3 months ago: Do not co-administer, alternate COVID-19 therapy advised. Non-cardiac indications where loss of anti-platelet activity may result in harm (e.g., stroke, peripheral vascular disease, neurosurgical interventions), specialist consultation is recommended.
○	Clopidogrel* (For Non-ACS indications)	Plavix®		Decreased exposure.	Co-administer with caution when used for other conditions.
⊘	Ticagrelor*	Brilinta®		Increased exposure.	Do not co-administer, unless ticagrelor can be safely held.

March 30, 2022

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
🚫	Statins (Atorvastatin, Lovastatin, Rosuvastatin, Simvastatin)	Lipitor®, Mevacor®, Crestor®, Zocor®	Statins	Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🚫	Lomitapide	Juxtapid®	Lipid-lowering agents	Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🚫	Colchicine	Myinfla®	Anti-gout	Increased exposure.	In renal/hepatic impairment: Do not co-administer, alternate COVID-19 therapy advised. In normal renal/hepatic function: Administer with caution. Dose reduction may be required depending on indication.
⚠	Amlodipine	Norvasc®	Antihypertensives	Increased exposure.	If practical, reduce dose by 50% or hold, monitor blood pressure, resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⚠	Felodipine	Plendil®		Increased exposure.	If practical, reduce dose by 50% or hold, monitor blood pressure, resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⚠	Nifedipine	Adalat®		Increased exposure.	If practical, reduce dose by 50% or hold, monitor BP, resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🚫	Diltiazem	Cardizem®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised if impractical to hold, switch or dose reduce. If practical, hold, switch or dose reduce by 50% and resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🚫	Verapamil	Isoptin®		Increased exposure.	Do not co-administer, alternate COVD-19- therapy advised if impractical to hold, switch or dose reduce. If practical, dose reduce by 50% and resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
✅	Timolol	Blocadren®		Increased exposure.	Co-administer.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
🟢	Angiotensin Receptor Blockers	*Multiple products		Irbesartan (Decreased exposure) Losartan, Valsartan, Sacubitril/Valsartan (Increased exposure) Candesartan, Olmesartan, Telmisartan (No interaction).	Co-administer.
🟢	Gliclazide	Diamicron®	Antihyperglycemics	Decreased exposure.	Co-administer.
🟢	Glimperide	Amaryl®		Decreased exposure.	Co-administer.
🟢	Canagliflozin	Invokana®		Decreased exposure.	Co-administer.
🟡	Repaglinide	Gluconorm®		Increased exposure.	Reduce the dose by 50%. Monitor blood glucose. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🟡	Saxagliptin	Onglyza®		Increased exposure.	Reduce the dose to 2.5 mg once daily if clinically appropriate. Monitor blood glucose. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🟢	Posaconazole	Posanol®	Anti-infectives	Increased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Co-administer.
🟡	Voriconazole	Vfend®		Decreased exposure.	Co-administer with caution, may require dose adjustments or increased monitoring.
🟡	Ketoconazole	Nizoral®		Increased exposure.	Co-administer with caution, may require dose adjustments or increased monitoring (maximum 200 mg/day).
🟡	Itraconazole	Sporanox®		Increased exposure.	Co-administer with caution, may require dose adjustments or increased monitoring (maximum 200 mg/day).

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
▲	Rifampin	Rofact®		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer if use within 14 days. Alternate COVID-19 therapy advised.
●	Rifabutin	Mycobutin®		Increased exposure.	Co-administer with caution, may require dose adjustments or increased monitoring (maximum 150 mg/day). Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
▲	Rifapentine	Priftin®		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer if use within 14 days. Alternate COVID-19 therapy advised.
●	Clarithromycin	Biaxin®		Increased exposure.	Co-administer with caution, may require dose adjustments for decreased renal function.
●	HIV Antiretrovirals	* Multiple classes and products	HIV Antiretrovirals	Increased exposure. Exception: Decreased exposure with raltegravir.	Co-administer.
▲	Glecaprevir/ Pibrentasvir	Maviret®	HCV DAAs	Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Carbamazepine	Tegretol®	Anticonvulsants	Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Eslicarbazepine	Aptiom®		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Oxcarbazepine	Trileptal®		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Phenobarbital	Phenobarb®		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Primidone	Mysoline®		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer, alternate COVID-19 therapy advised.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
▲	Phenytoin	Dilantin®		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer, alternate COVID-19 therapy advised.
●	Lamotrigine	Lamictal®		Decreased exposure.	Co-administer with caution. Limited utility of monitoring serum levels; consider if potential risk of decrease in serum levels is clinically important, depending on indication (i.e., seizures, vs. mood stabilizing indications).
●	Valproic Acid/Divalproex	Epival®/ Depakote®		Decreased exposure.	Co-administer with caution. Limited utility of monitoring serum levels; consider if potential risk of decrease in serum levels is clinically important, depending on indication (ie., seizures, vs. mood stabilizing indications).
●	Amitriptyline	Elavil®	Antidepressants	Increased exposure.	Co-administer.
●	Clomipramine	Anafranil®		Increased exposure.	Co-administer, caution in patients with multiple risk factors for QTc prolongation.
●	Fluoxetine	Prozac®		Increased exposure.	Co-administer.
●	Fluvoxamine	Luvox®		Increased exposure.	Co-administer.
●	Imipramine	Tofranil®		Increased exposure.	Co-administer.
●	Nortriptyline	Aventyl®		Increased exposure.	Co-administer.
●	Paroxetine	Paxil®		Increased OR decreased exposure.	Co-administer.
●	Sertraline	Zoloft®		Increased OR decreased exposure.	Co-administer.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
🟢	Trimipramine	Surmontil®		Increased exposure.	Co-administer.
🟢	Venlafaxine	Effexor®		Increased exposure.	Co-administer.
🟡	Mirtazapine	Remeron®		Increased exposure.	Reduce the dose to 15 mg/day. Resume regular dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🟢	Desipramine	Norpramin®		Increased exposure.	Co-administer.
🟡	Trazodone	Desyrel®		Increased exposure.	Reduce the dose by 50% if > 150 mg/day. Resume regular dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🟢	Bupropion	Welbutrin®, Zyban®		Decreased exposure.	Co-administer.
🟢	Vortioxetine	Trintellix®		Increased exposure.	Co-administer.
🟢	Citalopram	Celexa®		Increased exposure.	Co-administer.
🟢	Doxepin	Sinequan®		Increased exposure.	Co-administer.
🟢	Duloxetine	Cymbalta®		Increased OR decreased exposure.	Co-administer.
🟢	Escitalopram	Cipralex®		Increased exposure.	Co-administer.
🟡	Levomilnacipran	Fetzima®		Increased exposure.	Co-administer with caution. Do not exceed 80 mg/day. Monitor for potential adverse reactions.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
O	Vilazodone	Vibryd®		Increased exposure.	Co-administer with caution. Do not exceed 20 mg/day. Monitor for potential adverse reactions.
▲	Lurasidone	Latuda®	Antipsychotics	Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Clozapine	Clozaril®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Pimozide	Orap®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
⊘	Quetiapine	Seroquel®		Increased exposure.	If used for sleep hold and resume regular dosing 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). If used as an antipsychotic at lower doses, consider reducing the dose and resume regular dosing 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Otherwise, do not co-administer, alternate COVID-19 therapy advised.
⊘	Risperidone	Risperdal®/ Risperidal Consta®		Increased exposure.	Oral: If practical, consider reducing dose by 25-50% and monitor for confusion, extrapyramidal symptoms and sedation. Resume usual dose 3 days after completing Nirmatrelvir/ritonavir (Paxlovid®). If impractical or with long acting injection - do not co-administer, alternate COVID-19 therapy advised.
⊘	Aripiprazole	Abilify®/ Abilify Maintenna®		Increased exposure.	Oral: If practical, consider reducing dose by 25-50% and monitor for confusion, extrapyramidal symptoms and sedation. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). If impractical- do not co-administer, alternate COVID-19 therapy advised.
O	Ziprasidone	Zeldox®		Increased exposure.	Co-administer with caution, monitor for dizziness, extrapyramidal symptoms, and sedation.
O	Paliperidone	Invega®/ Invega Systena®/ Invega Trinza®		Increased exposure.	Co-administer with caution, monitor for dizziness, extrapyramidal symptoms, and sedation.
O	Haloperidol	Haldol®		Increased exposure.	Co-administer with caution, monitor for dizziness, extrapyramidal symptoms and sedation.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
⛔	Clonazepam	Rivotril®	Benzodiazepines/Sedatives	Increased exposure.	Co-administer if practical to modify/hold clonazepam: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Reduce dose by 25-50% and monitor for sedative effects or withdrawal effects. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Change therapy to lorazepam, oxazepam or temazepam. Resume clonazepam 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⛔	Diazepam	Valium®		Increased OR decreased exposure.	Co-administer if practical to hold/modify diazepam therapy: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Reduce dose by 25-50% and monitor for sedative effects or withdrawal effects. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Change therapy to lorazepam, oxazepam or temazepam. Resume diazepam 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⛔	Midazolam	Versed®		Increased exposure.	Oral: Do not co-administer, alternate COVID-19 therapy advised. Parenteral: Consider dose reduction and monitor for increased and prolonged sedation. Typical dose can be resumed 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⛔	Flurazepam	Dalmane®		Increased exposure.	Co-administer if practical to hold/modify flurazepam therapy: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Reduce dose by 25-50% and monitor for sedative effects or withdrawal effects. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Change therapy to lorazepam, oxazepam or temazepam. Resume flurazepam 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⛔	Clorazepate	Tranxene®		Increased exposure.	Co-administer if practical to hold/modify clorazepate therapy: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Reduce dose by 25-50% and monitor for sedative effects or withdrawal effects. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Change therapy to lorazepam, oxazepam or temazepam. Resume clorazepate 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
🚫	Triazolam	Halcion®		Increased exposure.	Co-administer if practical to hold/modify triazolam therapy: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Reduce dose by 25-50% and monitor for sedative effects or withdrawal effects. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Change therapy to lorazepam, oxazepam or temazepam. Resume triazolam 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🚫	Alprazolam	Xanax®		Increased exposure.	Co-administer if practical to hold/modify alprazolam therapy: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Reduce dose by 25-50% and monitor for sedative effects or withdrawal effects. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Change therapy to lorazepam, oxazepam or temazepam for 8 days.
🚫	Buspirone	Buspar®		Increased exposure.	Co-administer if practical to hold/modify buspirone therapy: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). -For patients taking 10-20 mg daily, reduce dose to 2.5 mg once to twice daily and monitor for sedative effects. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🚫	Zolpidem	Sublinox®		Increased exposure.	Co-administer if practical to hold/modify zolpidem therapy: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Reduce dose by 50% and resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🚫	Eszopiclone	Lunesta®		Increased exposure.	Reduce the dose to 2 mg/day. Resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
🚫	Zopiclone	Imovane®		Increased exposure.	Co-administer if practical to hold/modify zopiclone therapy: Hold and restart 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). Reduce dose by 50% and resume usual dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⚠	Clobazam	Frisium®		Increased OR decreased exposure.	Co-administer with caution, consider dose reduction and monitor for adverse effects.
⚠	Hydroxyzine	Atarax®		Increased exposure.	Co-administer with caution, consider dose reduction if patient is taking higher doses. Monitor for adverse effects.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
●	Bromazepam	Lectopam®		Increased exposure.	Co-administer.
●	Lorazepam	Ativan®		No change.	Co-administer.
●	Oxazepam	Serax®		No change.	Co-administer.
●	Temazepam	Restoril®		No change.	Co-administer.
●	Mycophenolate	Cellcept®	Antirejection agents	Increased exposure.	Co-administer.
▲	Calcineurin Inhibitors (Cyclosporin, Tacrolimus)	Neoral®, Prograf®, Advograf®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	mTOR Inhibitors (Everolimus, Sirolimus)	Afinitor®, Rapamune®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
⊘	Domperidone	Motilium®	Gastrointestinal Agents	Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). If practical, consider assessing risk of QTc prolongation.
⊘	Cisapride	Prepulsid®		Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). If practical, consider assessing risk of QTc prolongation.
▲	Ergot derivatives (Dihydroergotamine, Ergonovine, Ergotamine)	*multiple products	Ergot derivatives	Increased exposure.	Do not co-administer. Consider alternative agents for migraine therapy.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
●	Elagolix	Orlissa®	Hormonal agents	Increased exposure. Possible decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Co-administer.
○	Combined oral contraceptives (esp. those containing Ethinyl Estradiol)	*Multiple products		Decreased exposure.	Co-administer. Use an effective alternative contraceptive method during treatment and until one menstrual cycle after stopping nirmatrelvir/ritonavir (Paxlovid®).
⊘	Abemaciclib	Verzenio®	Oncology agents	Increased exposure.	Consult specialist. Hold if appropriate. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
▲	Apalutamide	Erleada®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
⊘	Dasatinib	Sprycel®		Increased exposure.	Consult specialist. Hold if appropriate. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⊘	Encorafenib	Braftovi®		Increased exposure.	Consult specialist. Hold if appropriate. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⊘	Ibrutinib	Imbruvica®		Increased exposure.	Consult specialist. Hold if appropriate. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
▲	Neratinib	Nerlynx®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
⊘	Nilotinib	Tasigna®		Increased exposure.	Consult specialist. Hold if appropriate. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
▲	Venetoclax	Venclexta®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
O	Vincristine	Vincristine®		Increased exposure.	Consult specialist. Co-administer with caution.
O	Vinblastine	Vinblastine®		Increased exposure.	Consult specialist. Co-administer with caution.
⊘	Ceritinib	Zykadia®		Increased exposure.	Consult specialist. Hold or reduce dose by 1/3 if appropriate. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
▲	Enzalutamide	Xtandi®		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer if current or recent use within 14 days, alternate COVID-19 therapy advised.
⊘	Fostamatinib	Tavalisse®		Increased exposure.	Consult specialist. Hold or reduce dose by 50% if appropriate. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⊘	Cyclophosphomide	Cytoxan®		Increased exposure.	Consult specialist. Hold or reduce dose if appropriate. Resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
▲	Fentanyl	n/a	Recreational Drugs	Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
O	Fentanyl	Duragesic®, Fentora™	Opioids	Increased exposure.	Co-administer with caution. Monitor for potential adverse reactions.
O	Tramadol	Ralivia®, Tridural®		Increased or decreased exposure.	Co-administer with caution. Monitor for potential adverse reactions or reduction in effect.
O	Methadone	Metadol®		Decreased exposure.	Co-administer with caution. Monitor for signs of withdrawal.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
O	Ecstasy MDMA (3,4-methylenedioxymethamphetamine)	n/a	Recreational Drugs	Increased exposure.	Co-administer with caution. Monitor for potential adverse reactions.
O	Hydrocodone	Hycodan®	Opioids	Increased or decreased exposure.	Co-administer with caution. Monitor for potential adverse reactions.
⊘	Meperidine	Demerol®		Increased exposure.	Hold or reduce dose by 50% if appropriate. Resume regular dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
O	Methamphetamine	n/a	Recreational Drugs	Increased exposure.	Co-administer with caution. Monitor for potential adverse reactions.
O	Oxycodone	Oxyneo®, Oxy IR®	Opioids	Increased exposure.	Reduce the dose by 50-75% and monitor for signs of sedation or respiratory depression. Resume regular dose 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
●	Modafinil	Provigil®	Stimulants	Increased or decreased exposure.	Co-administer.

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
▲	Sildenafil (For PAH)	Revatio®	Pulmonary antihypertensive	Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Tadalafil (For PAH)	Adcirca®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Bosentan	Tracleer®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
▲	Macitentan	Opsumit®		Increased exposure.	Do not co-administer, alternate COVID-19 therapy advised.
⛔	Sildenafil (For ED)	Viagra®	Vasodilators	Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⛔	Vardenafil (For ED)	Levitra®		Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).
⛔	Tadalafil (For ED)	Cialis®		Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®).

Nirmatrelvir/Ritonavir (Paxlovid®) Drug Interaction Assessment Tool

The safety and efficacy of nirmatrelvir/ritonavir (Paxlovid®) should be assessed in an individualized, patient-centric manner.
This tool is intended to provide guidance and does not replace clinical judgement.

Severity	Drug	Brand Name	Class	Effect on the drug co-administered with nirmatrelvir/ritonavir (Paxlovid®) *unless otherwise specified	Conclusion
⛔	Salmeterol	Advair® Serevent®	Respiratory agents	Increased exposure.	Hold and resume 3 days after completing nirmatrelvir/ritonavir (Paxlovid®). If unable to hold, use an ICS/LABA inhaler containing alternative long-acting beta-2-agonist.
🟢	Theophylline	Theo ER®		Decreased exposure.	Co-administer.
🟢	Systemic/inhaled Corticosteroids (Budesonide, Fluticasone, Triamcinolone, Dexamethasone, Prednisone, Methylprednisolone, Hydrocortisone)	*Multiple products	Systemic/Inhaled Corticosteroids	Increased exposure.	Co-administer. Note: If used in doses equivalent to dexamethasone < 12 mg/day.
▲	St. John's Wort	* Multiple brand names	Supplements	Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Do not co-administer if current or recent use within 28 days, alternate COVID-19 therapy advised.
🟢	Vitamin D	* Multiple brand names		Decreased nirmatrelvir/ritonavir (Paxlovid®) exposure.	Co-administer.