Nirmatrelvir/Ritonavir (Paxlovid™) - Tip Sheet for Drug-Interactions

*****Tables are NOT Exhaustive and Represent SHC/National Most Commonly Prescribed Drugs*****

For drugs not listed, check DDIs using resources below, particularly the Liverpool tool, for more information. Consider consulting specialist and/or clinical pharmacist.

Background and Basis for Potential Drug Interactions

Paxlovid™ received an emergency use authorization (EUA) from the US Food and Drug Administration (FDA) on December 22, 2021.[1] This medication is comprised of nirmatrelvir, a SARS-CoV-2 protease inhibitor and CYP3A4 substrate, and ritonavir, a strong CYP3A4 and P-gp inhibitor, weak CYP2D6 inhibitor, moderate CYP2B6 inducer, and weak CYP1A2, CYP2C19, and CYP2C9 inducer. The EUA allows Paxlovid™ to be used in adults and pediatric patients (12 years and older weighing at least 40 kg) with positive SARS-CoV-2 viral testing and a high risk of progression to severe COVID-19 infection.[2]

Paxlovid™ is an oral medication and is dosed 300 mg of nirmatrelvir (two 150 mg tablets) and 100 mg of ritonavir (one 100 mg tablet). For patients without kidney dysfunction (eGFR ≥ 60) all three tablets are taken together twice daily for 5 days.[2]

While ritonavir has no activity against SARS-CoV-2, it is used to boost nirmatrelvir levels.[2] Because of ritonavir's potent CYP3A and P-gp inhibition, it carries significant drug-drug interactions (DDIs) with many other medications. The anticipated onset of CYP3A inhibition by ritonavir is approximately 48 hours with an offset of 2 to 5 days after discontinuation.[3-5] Because of the short course of Paxlovid™, the induction properties of ritonavir are less likely to be clinically relevant. Read more on metabolism and DDIs here (link).[6]

Recommended Resources for Providers to Assess Potential DDIs:

- American Society of Transplantation Statement on Oral COVID-19 Antivirals
- FDA Paxlovid™ Fact Sheet for Healthcare Providers
- Liverpool COVID-19 Drug Interactions Checker
- Liverpool HIV Drug Interactions Checker
- Liverpool Protease Inhibitors Interaction Summary Table
- NIH Statement on Paxlovid Drug-Drug Interactions

Table 1. Commonly Prescribed Drugs Contraindicated with Nirmaltrelvir/Ritonavir

*****Tables are NOT Exhaustive and Represent SHC/National Most Commonly Prescribed Drugs*****

Prescribe Alternative COVID-19 Therapy	Withhold or Use Alternative Therapy† or Use Alternative COVID-19 Therapy
Amiodarone (X)	**Alprazolam (†)**
Apixaban (X)	**Antineoplastics (X†)**
Carbamazepine (X)	**Atorvastatin (†)**
Clopidogrel (X)	**Everolimus (X)**
Colchicine (X)	**Fentanyl (†)**
Phenobarbital (X)	**Isavuconazole (†)**
Phenytoin (X)	**Oral contraceptives (†)**
Rifampin (X)	**Quetiapine (†)**
Rivaroxaban (X)	**Rosuvastatin (†)**
Sildenafil (X†)*	**Simvastatin (X)**
Tadalafil (X†)*	**Sirolimus (X)**
Ticagrelor (X)	**Voriconazole (X)**

Key: X = absolute contraindication, † Consider using "Look for alternatives" functionality of Liverpool HIV Drug Interactions Checker searching under drug name "ritonavir".

*Absolute contraindication for pulmonary hypertension, if used for erectile dysfunction withhold medication

Table 2. Top SHC/Nationally-Prescribed Non-Contraindicated Drug Interactions with Nirmatrelvir/Ritonavir[7]

*****Tables are NOT Exhaustive and Represent SHC/National Most Commonly Prescribed Drugs*****

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments from FDA EUA HCP Fact Sheet and/or Liverpool
Amlodipine	↑ Amlodipine	Based on DDI studies with amlodipine and indinavir/ritonavir or paritaprevir/ritonavir, amlodipine exposure is expected to increase by ~2-fold. Reduce amlodipine dose by 50% when coadministered with nirmatrelvir/ritonavir and for a further 2 days after the last dose of nirmatrelvir/ritonavir.
Bupropion	↓ Bupropion	Concurrent administration of bupropion with repeated doses of ritonavir 100mg is expected to decrease bupropion level to a limited extent. Since duration of treatment for nirmatrelvir/ritonavir is short and maximal reduction effect expected after several days of concomitant therapy, no empiric dose adjustment is recommended. Monitor for decreased bupropion efficacy.
Clonazepam	↑ Clonazepam	Inhibition of CYP3A4 by ritonavir may increase clonazepam concentrations and a decrease in dose may be necessary. Monitor therapy for adverse drug effects due to increased serum concentrations of clonazepam.
Cyclosporine	↑ Cyclosporine	Cyclosporine is metabolized by CYP3A4 and plasma concentrations of cyclosporine are expected to increase when administered with nirmatrelvir/ritonavir. In a statement from the American Society of Transplantation, they recommend to significantly reduce the dose to 20% of the current dose.[8] For solid organ transplant recipients, reach out to the solid organ transplant provider for guidance. Therapeutic monitoring is recommended for immunosuppressants. For all other indications, consultation with an expert (e.g. clinical pharmacist, HIV specialist, and/or patient's specialist provider) should be considered. Avoid use of nirmatrelvir/ritonavir when close monitoring of immunosuppressant serum concentrations is not feasible.
Hydrocodone	↑ Hydrocodone ↓ Active metabolites	Hydrocodone is metabolized by CYP2D6 to hydromorphone and by CYP3A4 to norhydrocodone. Inhibition of CYP3A4 and CYP2D6 by nirmatrelvir/ritonavir may increase hydrocodone concentrations but decrease concentrations of norhydrocodone and hydromorphone. Monitor the analgesic effect and signs of opiate toxicity.

Itraconazole	↑ Paxlovid™	Itraconazole is metabolized by CYP3A4 and is a strong inhibitor of CYP3A4. Coadministration of itraconazole (200 mg once daily) and nirmatrelvir/ritonavir (300/100 mg twice daily) increased nirmatrelvir AUC and Cmax by 39% and 19%. High doses of itraconazole (>200 mg/day) are not recommended.
Levothyroxine	↓ Levothyroxine	The induction of glucuronidation by ritonavir increases the elimination of levothyroxine. However, no significant interaction is expected given the short treatment course of nirmatrelvir/ritonavir. Monitor therapy for signs and symptoms of hypothyroidism.
Mirtazapine	↑ Mirtazapine	Mirtazapine is metabolized by CYP3A4 and coadministration could increase mirtazapine concentrations. Use with caution as mirtazapine has been shown to prolong the QT interval, clinical monitoring including ECG assessment should be considered.
Oxycodone	↑ Oxycodone ↓ Active metabolites	Oxycodone is metabolized to noroxycodone via CYP3A4 and oxymorphone via CYP2D6. Concentrations of oxycodone may increase due to CYP3A4 inhibition by ritonavir. A dose reduction of oxycodone may be required to prevent opioid-related adverse effects with clinical monitoring. Monitor the analgesic effect and signs of opiate toxicity.
Posaconazole	↑ Paxlovid™	Coadministration has not been studied. Posaconazole is not significantly metabolized and eliminated mainly as unchanged drug in the feces. Approximately 17% of posaconazole undergo non-CYP mediated metabolism (hepatic glucuronidation by UGT1A4). Posaconazole is a strong inhibitor of CYP3A4 and could potentially increase nirmatrelvir/ritonavir exposure, although to a limited extent.
Prednisone	↑ Active metabolite	Prednisolone, the active metabolite of prednisone, is metabolized by CYP3A4. Coadministration with nirmatrelvir/ritonavir is expected to increase exposure of the prednisolone. Given the 5-day duration of nirmatrelvir/ritonavir this is unlikely to be clinically significant. Monitor therapy for adverse drug effects such as Cushing's syndrome and adrenal suppression.
Quetiapine	↑ Quetiapine	Consider therapy modification or dose reduction of quetiapine when combined with a strong CYP3A4 inhibitor. If initiating therapy start at the lowest dose and up-titrate cautiously.

Risperidone	↑ Risperidone	Risperidone is partly metabolized by CYP3A4 and substrate of P-gp. Nirmatrelvir/ritonavir could increase risperidone exposure. Use with caution and monitor closely for adverse effects such as malignant syndrome, extrapyramidal syndrome, and angioedema.
Tacrolimus	↑ Tacrolimus	Tacrolimus is metabolized by CYP3A4 and is a substrate of P-gp. Consider alternative COVID-19 therapies, if coadministration is unavoidable expect profoundly increased plasma concentrations of tacrolimus. Micelli et al, Mertz et al, and Lange et al, suggest intense dose reduction and/or withholding tacrolimus during all or part of duration while receiving concomitant ritonavir, alongside close therapeutic monitoring to guide dosing.[11,12] In a statement from the American Society of Transplantation, they recommend to hold or substantially reduce the dose, for HIV patients on ritonavir, doses of tacrolimus 0.5 mg per week have been used.[8] Some have proposed holding tacrolimus and to measure a level on day 3 to assess whether a one-time tacrolimus dose is needed during nirmatrelvir/ritonavir treatment.[13] For solid organ transplant recipients, reach out to the solid organ transplant provider for guidance. For all other indications, consultation with an expert (e.g. clinical pharmacist, HIV specialist, and/or patient's specialist provider) should be considered, any decision to hold tacrolimus should be made in discussion with the transplant provider or clinical specialist. Avoid use of nirmatrelvir/ritonavir when close monitoring of immunosuppressant serum concentrations is not feasible. TAT for tacrolimus levels at the SHC lab is 24hr (routine); 1 hr (STAT).[14]
Tamsulosin	↑ Tamsulosin	Tamsulosin is metabolized mainly by CYP3A4 and coadministration may increase tamsulosin exposure. Given tamsulosin's higher affinity for prostatic smooth muscle and its demonstrated tolerability when combined with other CYP3A4/CYP2D6 inhibitors, consider using tamsulosin at 0.4 mg/day if coadministered. Monitor blood pressure.
Tramadol	↑↓ Tramadol	Nirmatrelvir/ritonavir may increase tramadol exposure but also reduce the conversion to the more potent active metabolite. Monitor the analgesic effect and signs of opiate toxicity.
Trazodone	↑ Trazodone	Combination therapy should be used with caution and a dose reduction of trazodone should be considered. In healthy volunteers, ritonavir 200 mg twice daily increased trazodone concentrations by more than two-fold. Monitor for adverse reactions such as nausea, dizziness, hypotension, syncope, and QTc prolongation.

Warfarin	↑↓ Warfarin	Warfarin is a mixture of enantiomers which are metabolized by different cytochromes. Co-administration may increase or decrease warfarin concentrations. Closely monitor INR if co-administration with warfarin is necessary. TAT for tacrolimus levels at the SHC lab is 4hr (routine); 1 hr (STAT).[14]
Zolpidem Tartrate	↑ Zolpidem Tartrate	Coadministration with ritonavir increased zolpidem AUC and Cmax by 28% and 22%. However, a dosage adjustment may not be necessary based on drug-drug interaction data with ketoconazole (a strong inhibitor). Patients should be informed that they may experience enhanced sedative effects.

References

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