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Drug-Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid) and Select Cardiovascular Medications

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More than two years into the COVID-19 pandemic, prevention of severe disease remains a key public health goal. In adult outpatients with mild-to-moderate COVID-19 who are at risk for severe disease, ritonavir-boosted nirmatrelvir (Paxlovid) is efficacious in preventing hospitalization and death,[1] and the Food and Drug Administration has granted emergency use authorization for this purpose.[2]

Ritonavir increases plasma concentrations of nirmatrelvir by inhibiting cytochrome P450 (CYP) 3A4. CYP 3A4 inhibition confers an increased risk of drug-drug interactions with medications from many classes, including agents used to treat cardiovascular disease. For some cardiovascular drugs, the risk of coadministration with nirmatrelvir/ritonavir is prohibitive. For others, close clinical or laboratory monitoring during coadministration is needed, and dose adjustments may be required.

For any patient receiving cardiovascular medications, shared decision-making affords a meaningful opportunity to consider the risks and benefits of nirmatrelvir/ritonavir therapy. Factors to weigh include the patient's risk of severe COVID-19, based on age, comorbidities, vaccination status, and prior infection, as well as the risks of altering the cardiovascular drug regimen. If the risk of interrupting therapy with a cardiovascular drug is likely to result in short-term harm – for instance, stopping a direct oral anticoagulant in a patient with atrial fibrillation and recent stroke, or stopping an antiarrhythmic drug in a patient with ventricular tachycardia – deferring treatment with nirmatrelvir/ritonavir and seeking alternative treatment options for COVID-19 may be prudent. Conversely, if the risk of severe COVID-19 is high and interrupting a cardiovascular medication is less likely to cause harm – for instance, temporarily stopping atorvastatin in a patient with chronic coronary artery disease and well-controlled dyslipidemia – treatment with nirmatrelvir/ritonavir may be reasonable.

The following table includes cardiovascular medications for which potential drug-drug interactions with nirmatrelvir/ritonavir exist. If a drug is not listed, one cannot assume that it can be safely coadministered with nirmatrelvir/ritonavir. Updates to the table will be made as further data emerge.

Drug-Drug Interactions with Nirmatrelvir/Ritonavir (Paxlovid) and Select Cardiovascular Medications

NOTE: Holding or reducing the dose of select cardiovascular medications and/or other special monitoring requirements are recommended during treatment with nirmaltrelvir/ritonavir (Paxlovid) and for 3 days thereafter (for a total of 8 days from the first nirmaltrelvir/ritonavir dose) unless directed otherwise. In those with advanced age or on medications with long half-lives, adjustment or withholding times may need to be longer.[3] Medications with a very sensitive or narrow therapeutic index may need to be resumed 10 days after the first nirmatrelvir/ritonavir dose.[3]

The recommendations below reflect circumstances when the benefits of administering nirmatrelvir/ritonavir outweigh the risks of temporary discontinuation or modification of interacting medications.

MEDICATION CLASS	GENERIC NAME (COMMON/BRAND NAME)	INTERACTION EFFECTS	MANAGEMENT RECOMMENDATIONS
Angiotensin-Converting Enzyme Inhibitors	Examples: Captopril (Capoten), Enalapril (Vasotec), Fosinopril, Lisinopril, Rampiril	No clinically significant interaction expected	Coadministration is acceptable
Angiotensin Receptor Blockers	Examples: Candesartan (Atacand), Losartan (Cozaar), Valsartan (Diovan), Telmisartan (Micardis)	No clinically significant interaction expected	Coadministration is acceptable
Angiotensin Receptor-Neprilysin Inhibitor	Sacubitril/Valsartan (Entresto)[3-4]	Potential increased risk of hypotension	Monitor closely during nirmatrelvir/ritonavir therapy
Antiarrhythmic Drugs	Amiodarone[3-5] Dofetilide (Tikosyn)[3-5] Disopyramide (Norpace)[3-5] Dronedarone (Multaq)[3-5] Flecainide (Tambocor)[3-5] Propafenone (Rythmol)[3-5] Quinidine[3-5]	Potential increased plasma concentration of the antiarrhythmic drug that may result in arrhythmias or other serious adverse effects	Avoid coadministration of nirmatrelvir/ritonavir with antiarrhythmic drug
Antianginals	Ranolazine (Ranexa)[3-5]	Increased concentration of ranolazine and potential increased risk of adverse effects	Avoid ranolazine while on nirmatrelvir/ritonavir therapy
Anticoagulants	Warfarin (Coumadin)[3-4]	Co-administration may increase or decrease warfarin concentration	Monitor INR closely during nirmatrelvir/ritonavir therapy
	Apixaban (Eliquis)[3-4] Dabigatran (Pradaxa)[3-5] Edoxaban (Savaysa)[3-4] Rivaroxaban (Xarelto)[3-5]	Concentration of DOACs are increased, potentially leading to increased risk of bleeding	Hold DOAC during nirmatrelvir/ritonavir therapy

MEDICATION CLASS	GENERIC NAME (COMMON/BRAND NAME)	INTERACTION EFFECTS	MANAGEMENT RECOMMENDATIONS
Anti-Inflammatory Drugs	Colchicine (Colcrys)[3-4]	Increased concentration of colchicine may result in serious adverse effects	Discontinue colchicine during nirmatrelvir/ritonavir therapy
Antiplatelet Agents	Cilostazol (Pletal)[3-4]	Potential for increased concentration of cilostazol	Discontinue during nirmatrelvir/ritonavir therapy or reduce the dose to 50 mg twice daily
	Clopidogrel (Plavix)[3-4]	Possible decreased antiplatelet effect with clopidogrel	Avoid coadministration within 6 weeks following stent placement or consider temporarily changing to an alternative $P2Y_{12}$ inhibitor (e.g., prasugrel) during nirmatrelvir/ritonavir therapy
	Ticagrelor (Brilinta)[3-4]	Potential for increased concentration of ticagrelor	Avoid coadministration; consider temporarily changing to an alternative $P2Y_{12}$ inhibitor (e.g., prasugrel) during nirmatrelvir/ritonavir therapy
	Prasugrel (Effient)[3-4]	No clinically significant interaction expected	May continue during nirmatrelvir/ritonavir therapy
Calcineurin Inhibitors	Cyclosporine (Gengraf, Sandostatin) [3-4,7]	Concentration of calcineurin inhibitors is greatly increased, with an increased risk of adverse effects	Hold cyclosporine starting 24 hours prior to initiation of nirmatrelvir/ritonavir therapy
	Tacrolimus XR (Envarsus)[3-4,7]		Hold tacrolimus starting 24 hours prior to initiation of nirmatrelvir/ritonavir therapy
	Tacrolimus (Prograf)[3-4,7]		Hold tacrolimus extended release starting 48 hours prior to initiation of nirmatrelvir/ritonavir therapy For all calcineurin inhibitors, begin checking levels 3 days after the last dose of nirmatrelvir/ritonavir therapy and adjust dose accordingly
Calcium Channel Blockers	Amlodipine (Norvasc)[3-5] Diltiazem (Cardizem, Cartia)[3-5] Felodipine (Plendil)[3-5] Nicardipine (Cardene)[3-5] Nifedipine (Procardia)[3-5] Verapamil (Calan)[3-4]	Concentration of calcium channel blockers may be increased, resulting in increased risk of hypotension and/or bradycardia depending upon the agent used	Caution is warranted and close monitoring is recommended; dose reduction may be needed

MEDICATION CLASS	GENERIC NAME (COMMON/BRAND NAME)	INTERACTION EFFECTS	MANAGEMENT RECOMMENDATIONS
Cholesterol Absorption Inhibitors	Ezetimibe (Zetia)[3]	No clinically significant interaction expected	May be continued during nirmatrelvir/ritonavir therapy
Cardiac Glycosides	Digoxin (Lanoxin)[3-5]	Concentration of digoxin may be increased	Monitor for symptoms of toxicity and obtain levels as clinically indicated
HMG-CoA Reductase Inhibitors (statins)	Atorvastatin[3-4] Lovastatin[3-5] Rosuvastatin[3-4] Simvastatin[3-5]	Concentration of statins may be increased, resulting in potentially increased risk of statin-associated muscle symptoms	Atorvastatin and rosuvastatin should be discontinued during nirmatrelvir/ritonavir therapy; no need to hold before or after Lovastatin and simvastatin should be discontinued at least 12 hours prior to nirmatrelvir/ritonavir therapy and held during the 5 days of treatment, along with 5 additional days following completion of nirmatrelvir/ritonavir therapy
	Pitavastatin[3-4] Pravastatin[3-4]	No clinically significant interaction expected	May be continued during nirmatrelvir/ritonavir therapy
Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel Inhibitors	Ivabradine (Corlanor)[3-4]	Concentration of ivabradine expected to increase with possible enhanced risk of bradycardia	Avoid coadministration of nirmatrelvir/ritonavir therapy with ivabradine
Mechanistic Target of Rapamycin (mTOR) Inhibitors	Everolimus (Zortress)[3-4,7] Sirolimus (Rapamycin)[3-4,7]	Concentration of mTOR inhibitors is greatly increased with increased risk of adverse effects	Hold starting 48 hours prior to initiation of nirmatrelvir/ritonavir therapy Begin checking levels 3 days after last dose of nirmatrelvir/ritonavir therapy and adjust dose accordingly
Microsomal Triglyceride Transfer Protein Inhibitor	Lomitapide (Juxtapid)[3,6]	Concentration of lomitapide is increased	Discontinue during nirmatrelvir/ritonavir therapy
Phosphodiesterase Type 5 Inhibitors	Sildenafil (Revatio)[3-5] Tadalafil (Cialis)[3-4] Vardenafil (Levitra)[3-4]	Concentration may be increased, with possible hypotension, syncope, and visual abnormalities	If using for pulmonary arterial hypertension, discontinue during nirmatrelvir/ritonavir therapy

MEDICATION CLASS	GENERIC NAME (COMMON/BRAND NAME)	INTERACTION EFFECTS	MANAGEMENT RECOMMENDATIONS
Potassium Sparing Diuretics	Eplerenone (Inspra)[3-4]	Concentration of eplerenone is expected to increase, with potential for higher risk of hyperkalemia	Discontinue during nirmatrelvir/ritonavir therapy
	Finerenone (Kerendia)[3-4]	Concentration of finenerone is expected to increase, with potential for higher risk of hyperkalemia	Discontinue during nirmatrelvir/ritonavir therapy
	Spironolactone (Aldactone)[3-4]	No clinically significant interaction expected	May be continued during nirmatrelvir/ritonavir therapy
Renin Inhibitors	Aliskiren (Tekturna)[3-4]	Concentration of aliskiren is increased, with an increased risk of adverse effects	Discontinue during nirmatrelvir/ritonavir therapy
Thrombin Receptor Antagonist	Vorapaxar (Zontivity)[3,6]	Concentration of vorapaxar may be increased	Discontinue during nirmatrelvir/ritonavir therapy
Vasopressin Antagonist	Tolvaptan (Samsca)[3-4]	Concentration of tolvaptan may be increased	Discontinue during nirmatrelvir/ritonavir therapy

DOAC, direct oral anticoagulant. *INR*, international normalized ratio.

References

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