

Nirmatrelvir/ Ritonavir (Paxlovid)

What Prescribers and Pharmacists Need to Know

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?

No peer-reviewed studies are available for analysis. However, the drug was approved based on data from the unpublished EPIC-HR study¹ which was done in unvaccinated high-risk patients prior to circulation of the Omicron variant.

Based on regulatory submissions, nirmatrelvir/ritonavir reduces hospitalization in adult outpatients (with laboratory-proven SARS-CoV-2 infection, who were not on supplemental oxygen, and who were within 5 days of symptom onset).

With Health Canada’s approval of nirmatrelvir/ritonavir, the Ontario Science Advisory Table has made a **conditional** recommendation that nirmatrelvir/ritonavir be used in COVID-19 patients who are not on supplemental oxygen but are at high risk of progression to moderate or severe COVID-19.²

This recommendation is based on incomplete data. It will be revised with the publication of peer-reviewed data.

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Who should receive nirmatrelvir/ritonavir?

Nirmatrelvir/ritonavir should only be offered to patients with COVID-19 (*ideally 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. It should not be offered to pregnant patients.

Nirmatrelvir/ritonavir should be offered **preferentially** to patients with mild COVID-19 at higher risk of severe disease or complications from COVID-19:

- Immunocompromised individuals, regardless of vaccination status
- Unvaccinated individuals[†] (only if also age ≥60 years, Indigenous and age ≥50 years, or age ≥50 years with one or more risk factors[‡] for severe illness)

In times of drug shortage, nirmatrelvir/ritonavir should be offered **preferentially** to patients with mild disease at highest risk of severe disease or complications from COVID-19:

- Immunocompromised individuals, regardless of vaccination status
- Unvaccinated individuals[†] (only if also age ≥70 years, Indigenous and age ≥60 years, or age ≥60 years with one or more risk factors[‡] for severe illness)

Nirmatrelvir/ritonavir should be deployed preferentially to regions where there are barriers to intravenous administration of other recommended outpatient therapies (i.e., sotrovimab, remdesivir).

[†]Unvaccinated is defined as individuals who have received one or zero doses of a COVID-19 vaccine.

[‡]Risk factors include obesity, dialysis or stage 5 kidney disease (eGFR <15 mL/min), diabetes, cerebral palsy, intellectual disability, sickle cell disease, active cancer treatment, solid organ or stem cell transplant recipients.

¹ <https://clinicaltrials.gov/ct2/show/NCT04960202>

*PCR = polymerase chain reaction

² Clinical practice guideline summary: recommended drugs and biologics in adult patients with COVID-19. Ontario COVID-19 Science Advisory Table. 2021; Version 9.0. <https://doi.org/10.47326/ocsat.cpg.2022.9.0>

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:

The dose is 1 each of nirmatrelvir 150 mg and ritonavir 100 mg, with both tablets taken together orally BID x 5 days.

eGFR[†] <30 mL/min:

Nirmatrelvir/ritonavir is not recommended.

Severe hepatic impairment (Child-Pugh Class C):

Nirmatrelvir/ritonavir is not recommended.

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 some side effects are not yet known, and that there are, but serious side effects may happen.

Click here for the Paxlovid product monograph



Or visit:

<https://covid-vaccine.canada.ca/info/pdf/paxlovid-com-en.pdf>

OUTDATED

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).
- 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.

Nirmatrelvir/ritonavir have many drug interactions. Refer to page 3 →

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 28 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 medication 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.

Clinically significant drug interactions with nirmatrelvir/ritonavir (Paxlovid):

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

Symbol	Interaction	Rationale	Recommendation
▲	Contraindicated	Do not coadminister due to risk of serious toxicity. 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).	Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.
⚠	Contraindicated (current and recent use within past 28 days)	Do not coadminister due to risk of serious toxicity. Only start nirmatrelvir/ritonavir if drug can be safely held or replaced.	Stop or replace this drug, and re-start 2 days after completing nirmatrelvir/ritonavir therapy.
●	Contraindicated (significant increase in drug concentrations expected)	Do not coadminister due to risk of serious toxicity. Ideally, only start nirmatrelvir/ritonavir if drug can be safely held or replaced. In some instances, dose-adjustment is possible (refer to product monograph).	Stop or replace this drug if possible. Specialist prescriber or pharmacist consultation is recommended.
◆	Significant increase in drug concentrations expected	Although mentioned in the monograph, interaction is not anticipated (e.g., minimal impact on certain metabolic pathways, wide therapeutic index, and short course of nirmatrelvir/ritonavir therapy).	Continue with standard dosing.
✓	Drug interaction not likely to be clinically relevant		

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| ◆ Abemaciclib (<i>Verzenio</i>) | ✓ Divalproex | ✓ Maraviroc | ● Salmeterol (<i>Serevent, Advair</i>) |
| ● Alfuzosin (<i>Xatral</i>) | ◆ Dofetilide | ◆ Meperidine (<i>Demerol</i>) | ✓ Sertraline |
| ◆ Alprazolam (<i>Xanax</i>) | ✓ Dronabinol | ✓ Methamphetamine | ◆ Sildenafil for ED [†] (<i>Viagra</i>) |
| ▲ Amiodarone | ▲ Dronedarone (<i>Multaq</i>) | ● Methylergonovine | ▲ Sildenafil for PAH* (<i>Revatio</i>) |
| ✓ Amitriptyline | ◆ Edoxaban (<i>Lixiana</i>) | ✓ Metoprolol | ◆ Silodosin (<i>Rapaflo</i>) |
| ◆ Amlodipine (<i>Norvasc</i>) | ◆ Elagolix (<i>Orilissa</i>) | ● Midazolam, oral | ● Simvastatin |
| ⚠ Apalutamide (<i>Eribada</i>) | ◆ Encorafenib (<i>Braftovi</i>) | ◆ Modafinil | ◆ Sirolimus (<i>Rapamune</i>) |
| ◆ Apixaban (<i>Eliquis</i>) | ⚠ Enzalutamide | ▲ Neratinib (<i>Nerlynx</i>) | ⚠ St. John's wort (<i>Hypericum perforatum</i>) |
| ◆ Aripiprazole (<i>Abilify</i>), oral | ● Ergonovine | ◆ Nicardipine | ◆ Tacrolimus (<i>Prograf, Advagraf, Evvarsol</i>) |
| ◆ Atorvastatin (<i>Lipitor</i>) | ● Ergotamine | ◆ Nifedipine | ◆ Tadalafil for ED [†] (<i>Cialis</i>) |
| ✓ Atovaquone | ✓ Escitalopram | ◆ Nilotinib (<i>Tasigna</i>) | ▲ Tadalafil for PAH* (<i>Adcirca</i>) |
| ▲ Bosentan (<i>Tracleer</i>) | ⚠ Eslicarbazepine | ◆ Nitrazepam (<i>Mogadon</i>) | ◆ Tamsulosin (<i>Flomax</i>) |
| ◆ Bromazepam | ◆ Estazolam | ✓ Nortriptyline | ✓ Theophylline |
| ✓ Budesonide | ✓ Ethinyl estradiol | ⚠ Oxcarbazepine | ● Ticagrelor (<i>Brilinta</i>) |
| ✓ Bupropion | ◆ Everolimus (<i>Afinitor</i>) | ◆ Oxycodone (<i>Percocet, OxyNEO</i>) | ✓ Timolol |
| ◆ Buspirone (<i>Buspar</i>) | ◆ Felodipine | ◆ Paliperidone (<i>Invega</i>) | ◆ Tramadol |
| ⚠ Carbamazepine (<i>Tegretol</i>) | ◆ Fentanyl (<i>Duragesic</i>) | ✓ Paroxetine | ● Triazolam (<i>Halcion</i>) |
| ◆ Ceritinib (<i>Zykadia</i>) | ▲ Flecainide | ⚠ Phenobarbital | ✓ Trimipramine |
| ● Cisapride | ✓ Fluoxetine | ⚠ Phenytoin (<i>Dilantin</i>) | ● Vardenafil (<i>Levitra</i>) for ED [†] |
| ✓ Citalopram | ◆ Flurazepam | ▲ Pimozide | ▲ Vardenafil (<i>Levitra</i>) for PAH* |
| ✓ Clarithromycin | ✓ Fluvoxamine | ⚠ Primidone | ▲ Venetoclax (<i>Venclexta</i>) |
| ✓ Clomipramine | ◆ Fostamatinib (<i>Tavalisse</i>) | ▲ Propafenone | ✓ Venlafaxine |
| ◆ Clonazepam | ◆ Glecaprevir/Pibrentasvir (<i>Mavyret</i>) | ◆ Propoxyphene | ◆ Verapamil |
| ◆ Clopidogrel (<i>Plavix</i>) | ◆ Hydrocodone | ◆ Quetiapine (<i>Seroquel</i>) | ◆ Vinblastine |
| ◆ Clorazepate | ◆ Ibuprofen (<i>Imbruvica</i>) | ▲ Quinidine | ◆ Vincristine |
| ▲ Clozapine (<i>Clozaril</i>) | ✓ Imipramine | ◆ Quinine | ✓ Voriconazole |
| ● Colchicine in renal/hepatic impairment | ✓ Itraconazole | ✓ Raltegravir | ◆ Warfarin |
| ◆ Cyclosporine (<i>Neoral</i>) | ✓ Ketoconazole | ▲ Ranolazine (<i>Corzyna</i>) | ◆ Ziprasidone (<i>Zeldox</i>) |
| ◆ Dasatinib (<i>Sprycel</i>) | ✓ Lamotrigine | ◆ Rifabutin | ◆ Zolpidem (<i>Sublinox, Ambien</i>) |
| ✓ Dexamethasone | ● Lomitapide (<i>Juxtapid</i>) | ⚠ Rifampin | ◆ Zopiclone (<i>Imovane</i>) |
| ◆ Diazepam (<i>Valium</i>) | ● Lovastatin | ⚠ Rifapentine | |
| ◆ Digoxin | ▲ Lurasidone (<i>Latuda</i>) | ◆ Risperidone | |
| ● Dihydroergotamine | ◆ Macitentan (<i>Opsumit</i>) | ● Rivaroxaban (<i>Xarelto</i>) | |
| ◆ Diltiazem (<i>Tiazac, Cardizem</i>) | ✓ Maprotiline | ◆ Rosuvastatin (<i>Crestor</i>) | |

*PAH = pulmonary arterial hypertension
†ED = erectile dysfunction

Additional information may be found in the prescribing monograph: <https://covid-vaccine.canada.ca/info/pdf/paxlovid-pm-en.pdf> or the University of Liverpool COVID-19 drug interaction checker: <https://www.covid19-druginteractions.org/>.