Nirmatrelvir plus Ritonavir (Paxlovid)

What Prescribers and Pharmacists Need to Know

Why is nirmatrelvir plus 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 hospitalisation, 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 inhibiting SARS-CoV2 replication. Ritonavir is not active against SARS-CoV-2 but is a “boosting agent” and potent CYP3A4 inhibitor which slows nirmatrelvir metabolism thereby increasing its concentration.

Nirmatrelvir plus ritonavir is a highly effective outpatient therapy based on available data but there is high risk of harm if drug interactions are not mitigated, see details page 2 and 3.

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

The TGA originally provisionally approved Paxlovid® based on data from a Phase 2 study which has recently been published (EPIC-HR study2) which was done in unvaccinated, high-risk patients prior to circulation of the Omicron variant.

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

The Therapeutic Goods Administration provisionally approved nirmatrelvir plus ritonavir in January 2022 and as at publication date, the National COVID-19 Clinical Evidence Taskforce has made a conditional recommendation that nirmatrelvir plus 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 who are unvaccinated or partially vaccinated with additional risk factors.²

Who should receive nirmatrelvir plus ritonavir?

Nirmatrelvir plus ritonavir should only be offered to patients with COVID-19 (ideally proven by PCR* or a provider-administered test), who are not on supplemental oxygen, and who are within 5 days of symptom onset.

Nirmatrelvir plus ritonavir is NOT recommended during pregnancy, in women of childbearing potential not using contraception or in paediatric patients under 18 years of age.

Provide a Paxlovid patient information leaflet and obtain patient consent prior to commencing therapy.

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

- Immunocompromised² individuals, regardless of vaccination status
- Australian or Torres Strait Islander patients > 35 years
- Age ≥ 60 years with one or more risk factors¹ for severe illness

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

- Immunocompromised² individuals, regardless of vaccination status.
- Unvaccinated individuals† and age greater than 75 years
- Unvaccinated and age greater than 65 years of age (or ATSI patients greater than 35 years), with additional risk factors.†

Nirmatrelvir plus ritonavir should be deployed preferentially to rural and remote 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 zero doses of a COVID-19
†Risk factors include diabetes (requiring medication), BMI ≥ 25 kg/m², cardiovascular disease, hypertension, chronic lung disease, chronic kidney disease, immunosuppressed (e.g. bone marrow or organ transplantation, primary immune deficiencies, prolonged use of immune-weakening medications), medically related technological dependence (e.g. CPAP not related to COVID-19), HIV positive (viral load < 400 copies/mL), neuro-developmental disorders (e.g. cerebral palsy, Down syndrome), cancer (other than localised skin cancer), sickle cell disease.

¹Highest risk immunocompromising conditions include: patients receiving / recently received B-cell depleting therapies. Bruton tyrosine kinase inhibitors, Chimeric antigen receptor T cell, JAK inhibitors, Sphingosine 1-phosphate receptor modulators, Anti-CD2 antibodies, Anti-thymocyte globulin, Post-hematopoietic stem cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication. Patients with hematologic malignancies who are on active therapy. Lung transplant recipients, Patients who are within 1 year of receiving a solid-organ transplant (other than lung transplant) or haematopoietic stem cell transplant. Solid-organ transplant recipients with recent treatment for acute rejection with T or B cell depleting agents. Patients with certain primary immunodeficiencies. Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm²

²PCR = polymerase chain reaction

¹ PCR - polymerase chain reaction

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

1 Paxlovid® consists of 2 medicines 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 plus ritonavir may be taken with or without food and must be swallowed whole (Do not crush or break tablets)

Special Dosing Considerations:
Renal Impairment
1. eGFR = 30 to 59 mL/minute:
The dose is reduced to:
   - 1 x nirmatrelvir 150 mg +1 x ritonavir 100 mg, with both tablets taken together orally bd for 5 days.
2. eGFR ≤ 30 mL/minute:
   - Nirmatrelvir plus ritonavir is NOT recommended.

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

What side effects should I be aware of?
Common side effects of nirmatrelvir plus ritonavir are generally mild and can include dysgeusia (taste disturbance), diarrhoea, 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.

What drug interactions should I consider before prescribing nirmatrelvir plus 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 plus 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 plus ritonavir and contribute to the development of drug resistance.

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

For patients taking ritonavir or cobicistat for HIV therapy – refer to the patient’s Infectious Disease Physician for advice.

It is important that the patient has been informed of potential drug interactions and that the patient has disclosed all treatments currently taken, as well as there is agreement that the patient will not take any other medications whilst on Paxlovid® (e.g. steroids or treatments for migraine or erectile dysfunction)

What if my patient is taking a drug that interacts with nirmatrelvir plus 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 plus ritonavir.

- If the patient takes an interacting drug that can be held, the medication starting the first day of nirmatrelvir plus ritonavir therapy, and resume 3 to 5 days after the last dose of nirmatrelvir plus 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 plus ritonavir have many drug interactions. Refer to page 3
Clinically significant drug interactions with nirmatrelvir plus 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.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Interaction</th>
<th>Rationale</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>!</td>
<td>Contraindicated</td>
<td>Do not co-administer 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).</td>
<td>Use alternative COVID agent. Do not use nirmatrelvir/ritonavir.</td>
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<tr>
<td>!</td>
<td>Contraindicated (current and recent use within past 28 days)</td>
<td>Do not co-administer due to risk of serious toxicity. Only start nirmatrelvir/ritonavir if drug can be safely withheld or replaced.</td>
<td>Stop or replace this drug, and re-start 3 to 5 days after completing nirmatrelvir/ritonavir</td>
</tr>
<tr>
<td>!</td>
<td>Contraindicated (significant increase in drug concentrations expected)</td>
<td>Try to avoid co-administering 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 information). Careful monitoring is recommended.</td>
<td>Stop or replace this drug if possible. Specialist prescriber or pharmacist consultation is recommended.</td>
</tr>
<tr>
<td>!</td>
<td>Significant increase in drug concentrations expected</td>
<td></td>
<td>Continue with standard dosing.</td>
</tr>
<tr>
<td>!</td>
<td>Drug interaction not likely to be clinically relevant</td>
<td>Although mentioned in the Product Information, interaction is not anticipated (e.g., minimal impact on certain metabolic pathways, wide therapeutic index, and short course of nirmatrelvir/ritonavir therapy). Monitoring is recommended.</td>
<td></td>
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</tbody>
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- Abemaciclib
- Acalabrutinib
- Afatinib
- Alfuzosin
- Alprazolam
- Amiodarone
- Amitriptyline
- Amiodipine
- Apalutamide
- Aripiprazole
- Atazanavir
- Atovalstatin
- Atovalpine
- Avanafil
- Bictegravir
- Bosentan
- Bromazepam
- Budesonide
- Buspirone
- Carbamazepine
- Ceritinib
- Ciclosporin
- Citalopram
- Clarithromycin
- Clopiramine
- Clonazepam
- Clopidogrel
- Clozapine
- Colchicine
- Dabigatran
- Darifenacin
- Darunavir
- Dasatinib
- Dexamethasone
- Diazepam
- Disopyramide
- Digoxin
- Diltiazem
- Domperidone
- Dronabinol
- Efavirenz
- Enzalutamide
- Escitalopram
- Ethinylestradiol
- Everolimus
- Felodipine
- Fentanyl
- Flecaïnide
- Floxetine
- Fluvoxamine
- Fosamprenavir
- Garlic
- Gliclazide/Pibrarentasvir
- Haloperidol
- Ibrutinib
- Imipramine
- Isavuconazole
- Itraconazole
- Ivabradine
- KetocaGaza
- Lamotrigine
- Lercanidipine
- Lidocaine
- Loratidine
- Lurasidone
- Macitentan
- Maraviroc
- Methadone
- Methamphetamine
- Methypridinesolone
- Metoprolol
- Midazolam
- Mirtazapine
- Modafinil
- Morphine
- Neratinib
- Nevirapine
- Nifedipine
- Nitritinib
- Nitrazepam
- Nortriptyline
- Oxcarbazepine
- Oxycodone
- Paliperidone
- Paroxetine
- Phenetermine
- Phenobarbitol
- Phenotoin
- Pimozone
- Piroxicam
- Prednisolone
- Primidone
- Quetiapine
- Quinidine
- Quinine
- Raltegravir
- Ranolazine
- Riciquigat
- Rifabutin
- Rifampicin
- Rifapentine
- Risperidone
- Rivaroxaban
- Rosuvastatin
- Salmeterol
- Saquinavir
- Saxagliptin
- Sertraline
- Sildenafil
- Sirolimus
- St. John’s wort
- Tacrolimus
- Tadalafil
- Tamsulosin
- Tenofovir
- Theophylline
- Ticagrelor
- Timolol
- Tipranavir
- Tramadol
- Triamcinolone
- Triazolam
- Vardenafil
- Venodolax
- Verapamil
- Vinblastine
- Vincristine
- Voriconazole
- Warfarin
- Ziprasidone
- Zidovudine
- Zolpidem
- Zopiclone

Additional information may be found in the Product Information: [Paxlovid Product Information](https://www.gov.uk) or the University of Liverpool COVID-19 drug interaction checker: [https://www.covid19-druginteractions.org/](https://www.covid19-druginteractions.org/).

*PAH = pulmonary arterial hypertension
*ED = erectile dysfunction

Adapted from [Science Table COVID-19 Advisory for Ontario, University of Waterloo, School of Pharmacy](https://www.uwaterloo.ca).