Government of **Western Australia**
Department of **Health**

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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 3 and 4.

Nirmatrelvir plus 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 plus ritonavir for COVID-19?

Paxlovid® was provided provisional registration by the Therapeutic Goods Administration in January 2022 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 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]

Current recommendations are for people who are at higher risk of primary vaccine failure (such as people who are immunocompromised) or have high risk of disease progression.

Who should receive nirmatrelvir plus ritonavir?

Nirmatrelvir plus ritonavir should only be offered to patients with COVID-19 *(ideally proven by PCR (polymerase chain reaction) 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 12 years of age. Consultation with a Paediatric Infectious Disease Specialist is strongly recommended for patient is between 12-18 years of age and weighing greater than 40 kg.

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

As per PBS listing, adults (18 years and over) are eligible for treatment with Nirmatrelvir plus ritonavir (Paxlovid) if patient:

As per Pharmaceutical Benefits Advisory Committee

- Has received a positive PCR or RAT result (RAT must be verified by medical practitioner); AND
- Has at least one sign or symptom* attributable to mild to moderate COVID-19 (i.e. do not require oxygen) and do not require hospitalisation at the time of prescribing; **AND**
- Is within five (5)* days of symptom onset; **AND**
- Is aged 50 years or over (Aboriginal or Torres Strait Islander 30 years or over) and at high risk **OR**
- Is ‘moderately or severely’ immunocompromised.
- *Can be started after a positive test in asymptomatic patients 70 years and over

High risk is defined as the presence of at least two of the following conditions:

- The patient is in residential aged care,
- The patient has disability with multiple comorbidities and/or frailty,
- Neurological conditions, including stroke and dementia, and demyelinating conditions
- Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease,
- Heart failure, coronary artery disease, cardiomyopathies,
- Obesity (BMI greater than 30 kg/m^2),
- Diabetes Types I and II, requiring medication for glycaemic control,
- Renal impairment (eGFR less than 60mL/min),
- Cirrhosis, or
- The patient has reduced, or lack of, access to higher level healthcare and lives in an area of geographic remoteness classified by the Modified Monash Model as Category 5 or above.

Moderately to severely immunocompromised patients are those with:

1. Any primary or acquired immunodeficiency including:
   a. Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders,
   b. Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months),
   c. Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency OR

2. Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received:
   a. Chemotherapy or whole-body radiotherapy,
   b. High-dose corticosteroids (greater than or equal to 20 mg of prednisone per day, or equivalent) for at least 14 days in a month, or pulse corticosteroid therapy,
   c. Biological agents and other treatments that deplete or inhibit B cell or T cell function (abatacept, anti-CD20 antibodies, BTK inhibitors, JAK inhibitors, sphingosine 1-phosphate receptor modulators, anti-CD52 antibodies, anti-complement antibodies, anti-thymocyte globulin),
   d. Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) including mycophenolate, methotrexate, leflunomide, azathioprine, 6-mercaptopurine (at least 1.5mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus) OR

3. Any significantly immunocompromising condition(s) where, in the last 12 months the patient has received rituximab,

4. Others with very high-risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies OR

5. People with disability with multiple comorbidities and/or frailty

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

¥eGFR = estimated glomerular filtration rate

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.

For further Paxlovid product information:

Visit:

- Paxlovid Product Information(tga.gov.au)
- WA COVID-19 Information for health professionals - under Clinical Guidelines

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 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 plus 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 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 4

Access to National Medical Stockpile Medicines

This medication is regulated by the National Medical Stockpile (NMS). Access to NMS stock for patients who do not meet PBS Eligibility requires completion of a **WA Emergency COVID-19 Treatment Approval for Nirmatrelvir plus ritonavir (Paxlovid®) Form** and confirmation by the prescriber that the patient fulfils required criteria. The request is then reviewed by an Infectious Disease Physician for eligibility and approval.

The Commonwealth Department of Health are working to target access to those most vulnerable including the elderly and those in aged care with the view to transition to the Pharmaceutical Benefits Scheme (PBS) arrangements as supply continues to grow. By law medicines can only be listed on the PBS following a positive recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC)."

This does not apply to Residential Aged Care Facilities and Aboriginal Community Controlled Health Organisations (ACCHOs) that have received stock directly from the Commonwealth. It is expected that stock management under these circumstances will be managed as per the Authorisation to supply or administer a poison COVID-19 Treatment – National Medical Stockpile

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.

Symbol	Interaction	Rationale	Recommendation
⚠	Contraindicated	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).	Use alternative COVID agent. Do not use nirmatrelvir/ ritonavir.
⚠ᵛ	Contraindicated (current and recent use within past 28 days)		
🛑	Contraindicated (significant increase in drug concentrations expected)	Do not co-administer due to risk of serious toxicity. Only start nirmatrelvir/ritonavir if drug can be safely withheld or replaced.	Stop or replace this drug, and re-start 3 to 5 days after completing nirmatrelvir/ritonavir
◆	Significant increase in drug concentrations expected	Try to avoid co-administering due to risk of serious toxicity. Ideally, onlystart 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.	Stop or replace this drug if possible. Specialist prescriber or pharmacist consultation is recommended.
✔	Drug interaction not likely to be clinically relevant	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.	Continue with standard dosing.

- ⚠ Abemaciclib
- ⚠ Acalabrutinib
- ◆ Afatinib
- ⚠ Alfuzosin
- ◆ Alprazolam
- ⚠ Amiodarone
- ✔ Amitriptyline
- ◆ Amlodipine
- ⚠ᵛ Apalutamide
- ◆ Apixaban
- ◆ Aripiprazole
- ◆ Atazanavir
- 🛑 Atorvastatin
- ⚠ Atovaquone
- ⚠ Avanafil
- ✔ Bictegravir
- ⚠ Bosentan
- ◆ Bromazepam
- ◆ Budesonide
- ✔ Bupropion
- ◆ Buspirone
- ⚠ᵛ Carbamazepine
- ⚠ Ceritinib
- ⚠ Ciclosporin
- ✔ Citalopram
- ⚠ Clarithromycin
- ✔ Clomipramine
- ⚠ Clonazepam
- ⚠ Clopidogrel
- ⚠ Clozapine
- ⚠ Colchicine
- ◆ Dabigatran
- ◆ Darifenacin
- ◆ Darunavir
- ⚠ Dasatinib
- ◆ Dexamethasone
- ⚠ Diazepam
- ⚠ Disopyramide
- ◆ Digoxin
- ◆ Diltiazem
- ⚠ Domperidone
- ✔ Dronabinol
- ⚠ Efavirenz
- 🛑 Encorafenib
- ⚠ᵛ Enzalutamide
- ⚠ Eplerenone
- ⚠ Eletriptan
- ⚠ Erythromycin
- ⚠ Ergometrine
- ⚠ Ergotamine
- ✔ Escitalopram
- ⚠ᵛ Eslicarbazepine
- ✔ Ethinylestradiol
- ⚠ Everolimus
- ⚠ Felodipine
- ◆ Fentanyl
- ⚠ Flecainide
- ✔ Fluoxetine
- ✔ Fluvoxamine
- ◆ Fosamprenavir
- ⚠ Garlic
- ⚠ Glecaprevir/Pibrentasvir
- ◆ Haloperidol
- ⚠ Ibrutinib
- ✔ Imipramine
- ⚠ Isavuconazole
- 🛑 Itraconazole
- ⚠ Ivabradine
- 🛑 Ketoconazole
- ◆ Lamotrigine
- ⚠ Lercanidipine
- ◆ Lidocaine
- ✔ Loratadine
- ⚠ Lurasidone
- ◆ Macitentan
- ✔ Maraviroc
- ◆ Methadone
- ✔ Methamphetamine
- ⚠ Methyprednisolone
- ✔ Metoprolol
- ◆ Midazolam
- ✔ Mirtazepine
- ⚠ Modafinil
- ◆ Morphine
- ⚠ Neratinib
- ✔ Nevirapine
- ◆ Nifedipine
- ⚠ Nilotinib
- ⚠ Nitrazepam
- ✔ Nortriptyline
- ⚠ᵛ Oxcarbazepine
- ◆ Oxycodone
- ◆ Paliperidone
- ✔ Paroxetine
- ⚠ Pethidine
- ⚠ᵛ Phenobarbital
- ⚠ᵛ Phenytoin
- ⚠ Pimozide
- ⚠ Piroxicam
- ◆ Prednisolone
- ⚠ᵛ Primidone
- ◆ Quetiapine
- ⚠ Quinidine
- ⚠ Quinine
- ✔ Raltegravir
- ⚠ Ranolazine
- ⚠ Riociguat
- ◆ Rifabutin
- ⚠ Rifampicin
- ⚠ᵛ Rifapentine
- ◆ Risperidone
- ⚠ Rivaroxaban
- 🛑 Rosuvastatin
- ⚠ Salmeterol
- ◆ Saquinavir
- ◆ Saxagliptin
- ✔ Sertraline
- ⚠ Sildenafil
- ◆ Silodosin
- 🛑 Simvastatin
- ⚠ Sirolimus
- ◆ Sofosbuvir +velpatasvir +voxilaprevir
- ◆ Solifenacin
- ⚠ᵛ St. John's wort
- ⚠ Tacrolimus
- ⚠ Tadalafil
- ⚠ Tamsulosin
- ✔ Tenofovir
- ✔ Theophylline
- ⚠ Ticagrelor
- ✔ Timolol
- ◆ Tipranavir
- ◆ Tramadol
- ◆ Triamcinolone
- 🛑 Triazolam
- ⚠ Vardenafil
- ⚠ Venetoclax
- ✔ Venlafaxine
- ◆ Verapamil
- ⚠ Vinblastine
- ⚠ Vincristine
- ⚠ Voriconazole
- ◆ Warfarin
- ◆ Ziprasidone
- ✔ Zidovudine
- ◆ Zolpidem
- ◆ Zopiclone

Adapted from *Science Table COVID-19 Advisory for Ontario, University of Waterloo, School of Pharmacy.*

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

1 TGA provisionally approves Pfizer Australia Pty Ltd's COVID-19 treatment nirmatrelvir + ritonavir (PAXLOVID) | Therapeutic Goods Administration (TGA)
2. Hammond et al. Oral Nirmatrelvir for High-Risk, Nonhospitalised Adults with COVID-19. NEJM 2022 Feb 16 https://pubmed.ncbi.nlm.nih.gov/35172054/
3. National COVID-19 Clinical Evidence Taskforce - Nirmatrelvir plus ritonavir (Paxlovid) https://app.magicapp.org/#/guideline/6047/section/94769