DRUG GUIDELINE

Use of nirmatrelvir and ritonavir tablets for COVID-19

Introduction[1]

Nirmatrelvir and ritonavir (Paxlovid™) is provisionally registered by the Therapeutic Goods Administration for use in Australia for the treatment of COVID-19. **Vaccination is the preferred and primary option for the prevention of COVID-19.**

Clinical trials for nirmatrelvir and ritonavir were conducted when the Delta variant of SARS-CoV-2 was in circulation. Clinical efficacy against the Omicron variant is not clear.

This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation and should be used in conjunction with the nirmatrelvir and ritonavir resources available here.

Drug class and mechanism of action[1,2]

Nirmatrelvir is an antiviral which prevents the replication of SARS-CoV-2, the causative virus of COVID-19. It achieves this by inhibiting the activity of the SARS-CoV-2 main protease, which is responsible for viral replication. Co-administration of nirmatrelvir with low dose ritonavir helps to slow the metabolism of nirmatrelvir, resulting in increased concentrations of nirmatrelvir for longer periods of time to help combat the virus.

Approved indications[1,3]

Use of nirmatrelvir and ritonavir in NSW must be in accordance with the ACI Model of Care. The information below is derived from the Approved Product Information and the National COVID-19 Clinical Evidence Taskforce recommendations and **may differ from restrictions currently in place in NSW**.

Treatment of COVID-19 in adults (aged 18 years and older) who do not require initiation of supplemental oxygen due to COVID-19 and are at increased risk of progression to hospitalisation or death.

Based on inclusion criteria of the Phase 2/3 EPIC-HR trial, the risk factors for disease progression in adults are:

- Age ≥ 60 years
- Overweight (BMI ≥ 25 kg/m^2)
- Type 1 or 2 diabetes mellitus (requiring medication)
- Cardiovascular disease (including hypertension)
- Chronic lung disease (including asthma)
- Current smoker
- Chronic kidney disease (eGFR ≥ 30 mL/min/1.73 m^2)
- Immunocompromised patients or patients on immunosuppressive treatment (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)
- Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome)
- Active cancer (other than localised skin cancer)
- Sickle cell disease

The efficacy of nirmatrelvir and ritonavir is unclear in partially or fully vaccinated individuals (individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial).

See ACI Model of Care for further advice on use in vaccinated patients.

Contraindications[1,2]

- Known allergy to nirmatrelvir, ritonavir or any of the excipients of this medicine (Nirmatrelvir: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate, hydroxy propyl methylcellulose, titanium dioxide, polyethylene glycol, iron oxide red. Ritonavir: copovidone, sorbitan laureate, silica, colloidal anhydrous, calcium hydrogen phosphate, anhydrous sodium stearyl fumarate, hypromellose, titanium dioxide, macrogol, hydroxy propyl cellulose, talc, silica, colloidal anhydrous, polysorbate 80).
- Severe renal impairment (eGFR < 30mL/min/1.73m^2).
- Severe hepatic impairment (Child-Pugh Class C).
- Safety and efficacy of nirmatrelvir and ritonavir in children and adolescents aged 18 years and younger have not yet been established, therefore use in these patients is not recommended.
- Co-administration with medications that are highly dependent on CYP3A for clearance and medications that are potent CYP3A inducers refer to Table 1 and Appendix 1.

Precautions[1,2]

- Risk of HIV-1 resistance development – as nirmatrelvir is co-administered with low dose ritonavir, there may be a risk of HIV-1 resistance development in patients with uncontrolled or undiagnosed HIV-1 infection.
- Hepatotoxicity – caution should be exercised when administering nirmatrevir and ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.
- See below section for information on women who are pregnant, breastfeeding or are of childbearing potential.

Drug interactions[1,4,5]

Nirmatrelvir and ritonavir has significant and complex drug-drug interaction potential, primarily due to the ritonavir component of the combination. **See Appendix 1 for detailed information.**

A thorough review of drug-drug interactions is required prior to prescribing nirmatrelvir and ritonavir, and multidisciplinary input (e.g., clinical pharmacist, specialist physician or Medicines information service) should be sought in complex cases. Resources such as Liverpool COVID-19 drug interactions tool and Micromedex drug interactions tool can be used to identify drug interactions in a patient taking nirmatrelvir and ritonavir.

Ritonavir is contraindicated with medications that are highly dependent on CYP3A for clearance (**see Appendix 1**) and medications that are potent CYP3A inducers (Table 1), where significantly reduced nirmatrelvir and ritonavir plasma concentrations may be associated with the potential for loss of virologic response and resistance. Nirmatrelvir and ritonavir cannot be started immediately after discontinuation of any of the following medications in Table 1 due to the delayed offset of the recently discontinued CYP3A inducer.

Table 1. Medications that are potent CYP3A inducers that will result in a decrease of nirmatrelvir and ritonavir concentration. Refer to Appendix 1 for the full list of drug interactions.
Apalutamide
Carbamazepine, phenytoin, phenobarbital
Rifampicin
St John's Wort (*Hypericum perforatum)*

Dose, timing and route of administration[1]

For adult patients with normal renal function, the recommended dosing is:

N**irmatrelvir 300 mg** (2 x 150 mg tablets) and **ritonavir 100 mg** (1 x 100 mg tablet) taken orally every 12 hours for five days.

Nirmatrelvir and ritonavir can be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

Nirmatrelvir and ritonavir should be started as soon as possible after a diagnosis of symptomatic COVID-19 has been made and within five days of symptoms onset.

Nirmatrelvir and ritonavir treatment should **not** be started in patients requiring hospitalisation due to severe or critical COVID-19. If a patient requires hospitalisation because of severe or critical COVID-19 after commencing treatment with nirmatrelvir and ritonavir, the patient may complete the full 5-day treatment course at the discretion of their healthcare provider.

Missed doses
If a dose of nirmatrelvir and ritonavir is missed within eight hours of the time it is usually taken, this dose should be taken as soon as remembered. If a dose is missed by more than eight hours, this dose should be skipped, and the next dose taken at the regular time. The dose should not be doubled up to make up for the missed doses of nirmatrelvir and ritonavir.

Dose adjustments
- In patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), the dose of nirmatrelvir should be reduced to 150 mg every 12 hours for five days to avoid increased toxicity due to over-exposure (this dose adjustment has not been clinically tested). The ritonavir dose should remain as 100 mg every 12 hours.
- Note: This medication is presented in five daily blisters. Each daily blister has two separated sections (for morning and evening) each containing two tablets of nirmatrelvir and one tablet of ritonavir. This corresponds to the daily administration at the standard dose. **For patients with moderate renal impairment, the dispensing pharmacist must remove one tablet of nirmatrelvir from both the morning and evening sections of each blister and discard these tablets** (further information has been provided to Pharmacy Departments).

Use in women who are pregnant, breastfeeding or of childbearing potential[1,2]

Pregnancy

- Nirmatrelvir and ritonavir is pregnancy category B3 – it is **not recommended** during pregnancy and in women of childbearing potential not using contraception.
- Women of childbearing potential should use effective contraception for the duration of treatment. Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. **Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method during treatment with nirmatrelvir and ritonavir, and for seven days after stopping the medication.**

Breastfeeding

- It is unknown whether nirmatrelvir; is present in human milk, affects human milk production, or has an effect on the breastfed infant.
- Limited published data report ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or its effect on milk production. A risk to the infant cannot be excluded.
- Based on this, breastfeeding should be discontinued during treatment with nirmatrelvir and ritonavir and for seven days after the last dose.

Presentation[1]

This medication is presented in five daily blisters. Each daily blister has two separate sections (one for morning, one for night) each containing two tablets of nirmatrelvir (150 mg) and one tablet of ritonavir (100 mg). There are 30 tablets in total, equivalent to a five-day course.

Storage and stability[1]

Store at room temperature below 25°C. Do not refrigerate or freeze.

Monitoring requirements[1]

- Monitor the patient for adverse effects (see *Adverse Effects* section below). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue and initiate appropriate medications and/or supportive care.

Adverse effects[1,2]

- As the proposed use is for a provisionally approved medicine which has no relevant post-marketing data, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use. Refer to the Product Information for a complete list of possible adverse effects.
- The most reported adverse reactions during treatment with nirmatrelvir and ritonavir were taste disturbance, diarrhoea and vomiting.

Reporting[1]

- Nirmatrelvir and ritonavir is subject to additional monitoring in Australia – this will allow rapid identification of new safety information. Healthcare professionals are asked to report any suspected adverse events to the TGA, Pfizer (drug sponsor) and via their facility's incident management system.
- For hospital-initiated treatment, Drug and Therapeutics Committee oversight in the access process will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines' use. Nirmatrelvir and ritonavir use and outcome reporting should occur as per local governance processes.

References

1. Therapeutic Goods Administration. Australian Product Information – Paxlovid (nirmatrelvir/ritonavir tablets) https://www.tga.gov.au/sites/default/files/paxlovid-pi.pdf. Published 2022. Accessed January 25, 2022.
2. U.S. Food and Drug Administration (FDA). Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid. Published December 2021. Accessed January 27, 2022.
3. Australian National COVID-19 Clinical Evidence Taskforce. (2021). Australian guidelines for clinical care of people with COVID-19. https://app.magicapp.org/#/guideline/L4Q5An/section/LA6kkM Published 2022. Accessed February 1, 2022.
4. University of Liverpool. COVID-19 Drug Interaction Checker. https://www.covid19-druginteractions.org/ Published 2020. Accessed January 25, 2022.
5. Australian Medicines Handbook. Ritonavir. https://amhonline.amh.net.au.acs.hcn.com.au/chapters/anti-infectives/antiretrovirals/hiv-protease-inhibitors/ritonavir. Published 2022. Accessed January 25, 2022.

APPENDIX 1 – Drug interactions

= co-administration with Paxlovid™ is **contraindicated**

Drug class	Drugs within class	Effect on concentration	Clinical comments
Alpha 1-adrenoreceptor antagonist	alfuzosin	↑ alfuzosin	Co-administration contraindicated due to potential hypotension.
Analgesics	pethidine, piroxicam	↑ pethidine ↑ piroxicam	Co-administration contraindicated – potential for serious respiratory depression or haematologic abnormalities.
	fentanyl	↑ fentanyl	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended.
	methadone	↓ methadone	Monitor methadone-maintained patients closely for withdrawal effects and adjust the methadone dose accordingly.
Antianginal	ranolazine	↑ ranolazine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions.
Antiarrhythmics	amiodarone, flecainide	↑ antiarrhythmic	Co-administration contraindicated due to potential for cardiac arrhythmias.
Antiarrhythmics	lidocaine (systemic)	↑ antiarrhythmic	Caution is warranted and therapeutic concentration monitoring is recommended if available.
Anticancer drugs	apalutamide	↓ nirmatrelvir/ ritonavir	Co-administration contraindicated due to potential loss of virologic response and resistance.

Drug class	Drugs within class	Effect on concentration	Clinical comments
	afatinib	↑ afatinib	Caution should be exercised.
	abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, neratinib, nilotinib, venetoclax, vinblastine, vincristine	↑ anticancer drug	Avoid co-administration of encorafenib due to potential risk of serious adverse events such as QT interval prolongation. Avoid use of neratinib, venetoclax or ibrutinib. Co-administration of vincristine and vinblastine may lead to significant haematologic or gastrointestinal side effects.
Anticoagulants	warfarin rivaroxaban	↑↓ warfarin ↑ rivaroxaban	Closely monitor INR. Increased bleeding risk with rivaroxaban. Avoid concomitant use.
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	↓ nirmatrelvir/ ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	Co-administration contraindicated due to potential loss of virologic response and resistance.
	lamotrigine	↓ lamotrigine	Careful monitoring of serum levels or therapeutic effects is recommended.
Antidepressants	amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline	↑ amitriptyline ↑ fluoxetine ↑ imipramine ↑ nortriptyline ↑ paroxetine ↑ sertraline	Careful monitoring of therapeutic and adverse effects is recommended.

Drug class	Drugs within class	Effect on concentration	Clinical comments
Antifungals	voriconazole, ketoconazole, isavuconazole, itraconazole	↓ voriconazole ↑ ketoconazole ↑ isavuconazole ↑ itraconazole ↑ nirmatrelvir/ritonavir	Avoid concomitant use of voriconazole. Monitor for adverse effects with ketoconazole, itraconazole and isavuconazole and reduce azole dose if required.
Anti-gout	colchicine	↑ colchicine	Co-administration contraindicated - potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Anti-HIV protease inhibitors	atazanavir, darunavir, fosamprenavir,saquinavir, tipranavir	↑ protease inhibitor	Patients on ritonavir- containing HIV regimens should continue their treatment as indicated. Monitor for increased Paxlovid™ or protease inhibitor adverse events. For further advice, consult your HIV specialist Physician or Pharmacist
Anti-HIV	efavirenz, maraviroc, nevirapine, raltegravir, zidovudine, bictegravir/ emtricitabine/tenofovir	↑ efavirenz ↑ maraviroc ↓ raltegravir ↓ zidovudine ↑ bictegravir ↔ emtricitabine ↑ tenofovir	For further advice, consult your HIV specialist Physician or Pharmacist
Antihistamine	loratadine	↑ loratadine	Careful monitoring of therapeutic and adverse effects is recommended.
Anti-infective	clarithromycin,erythromycin	↑ clarithromycin ↑ erythromycin	Monitor for adverse effects and reduce macrolide dose if required. Consider changing to azithromycin if appropriate.

Drug class	Drugs within class	Effect on concentration	Clinical comments
	atovaquone	↓ atovaquone	Careful monitoring of serum levels or therapeutic effects isrecommended.
Antimycobacterial	rifampicin	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and resistance. Alternative antimycobacterial drugs such as rifabutin should be considered.
	rifabutin	↑ rifabutin	Reduction of rifabutin dose to 150 mg daily in the presence of nirmatrelvir/ritonavir may be indicated.
Antipsychotics	lurasidone, clozapine	↑ lurasidone ↑ clozapine	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias.
	quetiapine	↑ quetiapine	If co-administration is necessary, reduce quetiapine dose and monitor for quetiapine-associated adverse reactions.
	haloperidol, risperidone	↑ haloperidol ↑ risperidone	Careful monitoring of therapeutic and adverse effects is recommended.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nifedipine	↑ calcium channel blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed.
Cardiac glycosides	digoxin	↑ digoxin	Caution should be exercised with appropriate monitoring of serum digoxin concentrations.
Endothelin receptor antagonists	bosentan	↑ bosentan	Discontinue use of bosentan at least 36 hours prior to initiation of Paxlovid™.
	riociguat	↑ riociguat	Co-administration is not recommended.
Ergot derivatives	ergometrine	↑ ergometrine	Co-administration is contraindicated.

Drug class	Drugs within class	Effect on concentration	Clinical comments
Hepatitis C direct acting antivirals	glecaprevir/ pibrentasvir sofosbuvir/ velpatasvir/ voxilaprevir	↑ antiviral	Not recommended to co-administer ritonavir with glecaprevir/pibrentasvir. Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased Paxlovid or HCV drug adverse events with concomitant use.
Herbal products	St. John's Wort (hypericum perforatum)	↓ nirmatrelvir/ritonavir	Co-administration contraindicated due to potential loss of virologic response and resistance.
HMG-CoA reductase inhibitors	simvastatin	↑ simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis. Discontinue use of simvastatin at least 12 hours prior to initiation of Paxlovid™.
	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Consider temporary discontinuation of atorvastatin and rosuvastatin during treatment with Paxlovid™.
Hormonal contraceptive	ethinylestradiol	↓ ethinylestradiol	An additional, non-hormonal method of contraception should be considered.
Immunosuppressants	ciclosporin, tacrolimus, sirolimus, everolimus	↑ ciclosporin ↑ tacrolimus ↑ sirolimus ↑ everolimus	Therapeutic concentration monitoring is recommended. Avoid use of Paxlovid when monitoring of immunosuppressant serum concentrations is not feasible. Avoid concomitant use of sirolimus and Paxlovid.
Long acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	Co-administration is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia.

Drug class	Drugs within class	Effect on concentration	Clinical comments
PDE5 inhibitor	Sildenafil, avanafil, tadalafil, vardenafil	↑ sildenafil ↑ avanafil ↑ tadalafil ↑ vardenafil	Co-administration contraindicated
Sedative/hypnotics	midazolam (administered parenterally)	↑ midazolam	Close clinical monitoring required in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.
	diazepam	↑ diazepam	Co-administration diazepam with ritonavir is contraindicated.
	alprazolam	↑ alprazolam	Caution is warranted during the first several days before induction of alprazolam metabolism develops.
Sleeping agent	zolpidem	↑ zolpidem	Monitoring for excessive sedative effects.
Smoking cessation	bupropion	↓ bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to bupropion.
Systemic corticosteroids	betamethasone, budesonide, dexamethasone, methylprednisolone, prednisone, triamcinolone	↑ corticosteroid	Increased risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids, including beclomethasone and prednisolone, should be considered.