DRUG GUIDELINE – NIRMATRELVIR+RITONAVIR (PAXLOVID®) FOR TREATMENT OF COVID-19

Nirmatrelvir+Ritonavir (Paxlovid®) is provisionally registered by the Therapeutic Goods Administration for use in Australia for the treatment of COVID-19 in adults 18 years of age 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. The decision has been made on the basis of short-term efficacy and safety data. Continued approval of this indication depends on the efficacy and safety data from ongoing clinical trials and post-market assessment.
Paxlovid® is not intended to be used as a substitute for vaccination again COVID-19.
The National COVID-19 Clinical Evidence Taskforce provides a conditional recommendation for use of Nirmatrelvir plus Ritonavir oral antiviral therapy within 5 days of symptom onset in unvaccinated adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression. This recommendation is based on the recently NEJM published trial Oral Nirmatrelvir for High-Risk, Nonhospitalised Adults with COVID-19 which is a single Phase 2/3, randomised, double-blind, placebo-controlled study in non-hospitalised symptomatic adult participants with a confirmed diagnosis of SARS-CoV-2 infection, comparing nirmatrelvir plus ritonavir with placebo in 2246 unvaccinated adults with PCR-confirmed COVID-19 and mild illness. Within this trial participants were treated with oral nirmatrelvir/ritonavir 300 mg/100 mg twice daily for 5 days.

As per the PBS Listing, adults (18 years and over) are eligible for treatment if the patient:

- 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 hospitalization at the time of prescribing; AND
- is within five (5) days of symptom onset; AND
- is aged 65 years or over (ATSI 50 years and over) and at high risk OR 'moderately or severely' immunocompromised.

The National COVID-19 Clinical Evidence Taskforce has provided conditional recommendation for Nirmatrelvir plus Ritonavir on the 9 May 2022 to include people older than 12 years old, weighing more than 40 kg, who have mild to moderate COVID-19, and who are at high risk of progression to severe symptoms, hospital admission, or death. (As per Paxlovid® FDA Fact Sheet for Health Professionals)

This medication is also available via the National Medical Stockpile (NMS) for cases where a prescriber considers treatment is clinically indicated but the patient is not eligible under the PBS. Access to NMS stock requires completion of a WA Emergency COVID-19 Treatment Declaration for Nirmatrelvir plus Ritonavir (Paxlovid®) Form and confirmation by the prescriber that the patient fulfils required criteria.

Ongoing supply of COVID-19 therapeutics via the NMS is uncertain and availability is expected to fluctuate with demand and constraints in the supply chain. To ensure equity of access and conserve Paxlovid® therapy for those patients at the highest risk of disease progression, a tiered access criterion is in place to allocate stock taking into account current supply.

This guideline should be used in conjunction with the Paxlovid® resources available:

- WA Emergency COVID-19 Treatment Approval for Nirmatrelvir+Ritonavir (Paxlovid®) Form
- Paxlovid® Patient Consent Form and further information regarding consent, and
- Paxlovid ® Patient Information Leaflet.
- WA Health Paxlovid Patient Information Leaflet

Drug Class[1,2]:

Nirmatrelvir is a SARS-CoV-2 main protease inhibitor (aka Mpro, 3CLpro, or nsp5 protease inhibitor) and ritonavir is a CYP3A inhibitor included to maintain nirmatrelvir plasma levels during treatment.

- Ritonavir alone has no activity against SARS-CoV-2

Clinical Criteria:

Within the patient population for which nirmatrelvir plus ritonavir (Paxlovid®) is recommended for use, decisions about the appropriateness of treatment should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

As per the PBS Listing, adults (18 years and over) are eligible for treatment with nirmatrelvir plus ritonavir (Paxlovid®) if the patient:

- 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 hospitalization at the time of prescribing; AND
- is within five (5) days of symptom onset; AND
- is aged 65 years or over (Aboriginal or Torres Strait Islander 50 years and over) and at high risk OR 'moderately or severely' immunocompromised.

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

- The patient has received less than 2 doses of SARS-CoV-2 vaccine,
- The patient is aged 75 years or over,
- The patient is in residential aged care or residential disability care,
- Neurological conditions, including stroke and dementia,
- Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis,
- Congestive heart failure (NYHA Class II or greater),
- Obesity (BMI greater than 30 kg/m2),
- Diabetes Types I and II, requiring medication for glycaemic control,
- Renal failure (eGFR less than 60mL/min),
- Cirrhosis,
- 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.

Immunosuppressed patients at high risk of severe disease

As per PBS listing, moderate to severely immunocompromised patients include:

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 (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 (more than 0.4mg/kg/week), leflunomide, azathioprine (at least 3mg/kg/day), 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, OR

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 severe intellectual or physical disabilities requiring residential care.

For patients not meeting PBS eligibility the National Taskforce Guidelines, people older than 12 years old, weighing more than 40 kg, who have mild to moderate COVID-19, and who are at high risk of progression to severe symptoms, hospital admission, or death. are eligible for Paxlovid® if they are:

Unvaccinated

- Unvaccinated
- within five (5) days of symptom onset; **AND**
- who have mild to moderate COVID-19 disease (i.e. do not require oxygen); **AND**
- who have **one or more of the following risk factors** for disease progression;

Adults:

Based on the population included within the trial, evidence demonstrates a reduction in hospitalisation when used in individuals with one or more of the following risk factors for disease progression:

- Age ≥ 60 years
- Diabetes (requiring medication)
- BMI ≥ 25 kg/m^2
- Cardiovascular disease
- Hypertension
- Chronic lung disease

There were insufficient numbers of participants with the following risk factors to determine the extent to which nirmatrelvir plus ritonavir impacts hospitalisation or death, however as these conditions frequently result in poorer outcomes for patients following SARS-CoV-2 infection, they will likely benefit from treatment:

- Chronic kidney disease (where the eGFR ≥ 30 mL/minute, dose adjustment is required ≥ 30-60mL/min)
- Immunosuppressed (e.g. bone marrow or organ transplantation, primary immune deficiencies, prolonged use of immune-weakening medications)
- Medical 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 syndrome)
- Cancer (other than localised skin cancer)
- Sickle cell disease
- Aboriginal and/or Torres Strait Islander patients > 35 years old.

Immunocompromised or multiple risk factors

In addition to at-risk unvaccinated adults, also consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen AND:

- are immunosuppressed or not immunocompetent regardless of vaccination status; OR
- have received one or two doses of vaccine and who are at high risk of severe disease on the basis of age and multiple risk factors.

There is no evidence evaluating the effectiveness of nirmatrelvir plus ritonavir in partially or fully vaccinated patients. Given this and the lower risk of deterioration in these patients, it is unlikely that nirmatrelvir plus ritonavir will be particularly valuable in patients who have received three doses of vaccine, unless the patient is immunosuppressed.

There is limited evidence on the effectiveness of nirmatrelvir plus ritonavir in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that nirmatrelvir plus ritonavir will be beneficial for immunosuppressed patients as per Recommendations on the use of a 3rd primary dose of COVID-19 vaccine in individuals who are severely immunocompromised (health.gov.au).

Severe immunocompromising conditions include:

- Patients who are within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving Bruton tyrosine kinase inhibitors

- Chimeric antigen receptor T cell recipients
- 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
    - PIDs affecting cellular and humoral immunity (severe and other combined immunodeficiencies (https://doi.org/10.1007/s10875-019-00737-x)
    - PIDs with profoundly decreased or absent B cell number or function
    - PIDs with impaired interferon responses
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm3
- Patients on any of the following agents not already listed
    - Anti-CD20 antibodies rituximab, obinutuzumab, ocrelizumab, ofatumumab
    - BTK inhibitors ibrutinib, acalabrutinib, zanubrutinib
    - Sphingosine 1- phosphate receptor modulators fingolimod, siponimod
    - Anti-CD52 antibodies alemtuzumab
    - Anti-complement antibodies eculizumab
    - Anti-thymocyte globulin

Contraindications:

- **Hypersensitivity:** Contraindicated in patients with known hypersensitivity to nirmatrelvir and/or ritonavir, or any of the excipients (Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, sodium stearylfumarate, Opadry complete film coating system 05B140011 Pink, copovidone, calcium hydrogen phosphate, sorbitan monolaurate, hypromellose, titanium dioxide, macrogol 400, hyprolose, macrogol 3350 and polysorbate 80.
- **Severe renal impairment** (eGFR < 30mL/min)
- **Severe hepatic impairment** (Child-Pugh Class C)
- **Drug interactions** that are associated with serious and/or life-threatening reactions and interactions that result in decrease in nirmatrelvir + ritonavir concentrations which may cause loss of virologic response and possible resistance.

Table 1: Medicinal products that are contraindicated or not recommended for concomitant use with Paxlovid®

Class of Medication	Medicinal products within class
Interactions that **result in an increase or decrease** in concentrations of concomitant medicine	
Alpha 1-adrenoreceptor antagonist	alfuzosin
Antiarrhythmics	amiodarone, disopyramide, flecainide, quinidine
Anticancer	acalabrutinib, neratinib, venetoclax, enzalutamide
Anticoagulants	rivaroxaban
Antiplatelets	clopidogrel (recently stented patients), ticagrelor
Anti-emetics	domperidone
Antifungals	voriconazole, isavuconazole
Anti-gout	colchicine
Antipsychotics	lurasidone, clozapine
Antivirals	glecaprevir with pibrentasvir
Bronchodilators	salmeterol
Ergot derivatives	ergometrine
Hypertension/ heart failure agents	bosentan, eplerenone, ivabradine, lercanidipine
Immunosuppressants	ciclosporin, everolimus, sirolimus, tacrolimus
Lipid-modifying agents HMG-CoA reductase inhibitors	simvastatin
Nonsteroidal anti-inflammatory drugs (NSAIDs)	piroxicam
Opioid analgesic	pethidine
PDE5 inhibitor	avanafil, sildenafil, vardenafil, tadalafil
Sedative/hypnotics	diazepam, clonazepam
Interactions that result in **decrease in nirmatrelvir/ritonavir concentrations** with associated potential loss of virologic response and possible resistance	
Anticancer	apalutamide
Anticonvulsants	carbamazepine, phenobarbital, phenytoin, primidone
Antimycobacterials	rifampicin
Herbal products	St. John's Wort (*Hypericum perforatum*)

Special Warnings and Precautions for Use:

- **Hepatotoxicity** - Hepatic transaminase elevations, clinical hepatitis and jaundice have occurred in patients receiving ritonavir. Therefore, caution should be exercised when administering Paxlovid® to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.

- **Moderate renal impairment (eGFR ≥30 to <60mL/min)** – Systemic exposure of nirmatrelvir increases in renally impaired patients. In patients with moderate renal impairment the dose of nirmatrelvir should be reduced from 300mg twice daily to 150mg twice daily (see 'Dose' section below).
- **Pregnancy and breastfeeding:** nirmatrelvir plus ritonavir is pregnancy category B3[1]. Paxlovid® is not recommended during pregnancy and in women of childbearing potential not using contraception. There are no human studies of the effects of Paxlovid® during pregnancy and women of childbearing potential should avoid becoming pregnant during treatment and for at least 7 days after stopping Paxlovid®.

  There are also no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Breast feeding should be discontinued during treatment and for 7 days after the last dose of Paxlovid®.
- **Paediatric population:** The safety and efficacy of nirmatrelvir/ritonavir has not been established in children <12 years of age or weighing <40 kg.

Drug Interactions:

Paxlovid® is an inhibitor of CYP3A and may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. Medicinal products that are extensively metabolised by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in exposure when co-administered with nirmatrelvir/ritonavir. Thus, co-administration of nirmatrelvir/ritonavir with medicinal products highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. (See Table 1)

See **Appendix 1** for list of potentially significant drug interactions with other medicines. This list also includes drug combinations that are not absolute contraindications but require consideration.

The University of Liverpool COVID-19 Drug Interactions checker can also be used to check for specific interactions between nirmatrelvir/ritonavir and other medications/medication classes.
https://www.covid19-druginteractions.org/checker

Presentation and Storage:

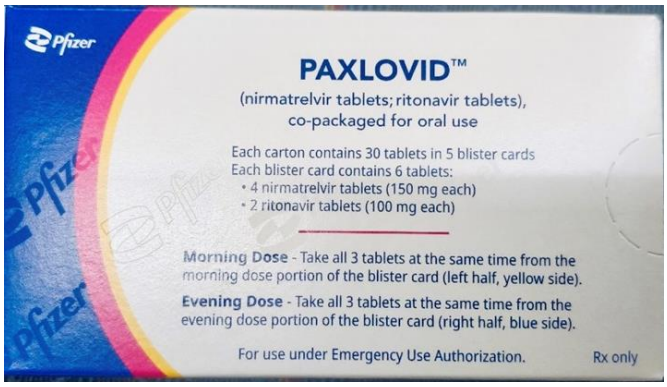
Store below 25°C.

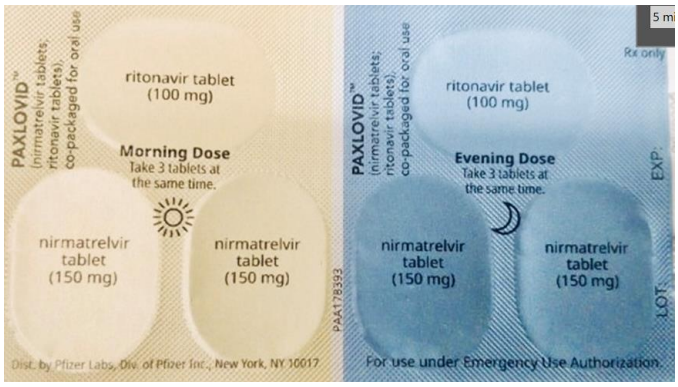
Nirmatrelvir

Nirmatrelvir tablets are oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side.

Ritonavir

Ritonavir tablets are white to off-white coated, oval tablets marked with the Abbott logo and "NK".





Dose:

Nirmatrelvir must be taken together with ritonavir. Failure to correctly take nirmatrelvir with ritonavir will result in plasma levels of nirmatrelvir that will be insufficient to achieve the desired therapeutic effect.

Both nirmatrelvir and ritonavir tablets can be taken with or without food.

The tablets should be swallowed whole and not chewed, broken, or crushed.

The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) taken together orally every 12 hours for 5 days.

No dosage adjustment is needed for patients with either mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

Dose adjustment in moderate renal failure (≥30 to <60 mL/min)

In patients with moderate renal impairment, the dose should be reduced to nirmatrelvir + ritonavir 150mg/100 mg (one 150mg tablet and one 100mg tablet) every 12 hours for 5 days to avoid increased toxicity due to over-exposure (this dose adjustment has not been clinically tested).

eGFR	Nirmatrelvir/ritonavir (Paxlovid®) Dose
Greater than 60 mL/minute (Normal renal function or mild renal impairment)	**300 mg** nirmatrelvir (two tablets) with 100 mg ritonavir (one tablet), taken twice daily for 5 days
≥ 30 to < 60 mL/minute (Moderate renal impairment)	**150 mg** nirmatrelvir (one tablet) with 100 mg ritonavir (one tablet), taken twice daily for 5 days
< 30mL/minute (Severe renal impairment)	**Contraindicated**

As a healthcare provider, you should:

- Determine the appropriate Paxlovid® dose for your patient
- Specify the numeric dose of each active ingredient (nirmatrelvir and ritonavir) in the Paxlovid® prescription
- Counsel patients with moderate renal impairment about renal dosing instructions and inform them that the blister cards will be altered by the pharmacist to remove unneeded tablets

Adverse Effects[1]:

It may be difficult to distinguish between adverse effects of Paxlovid® and signs and symptoms of COVID-19. Adverse effects related to nirmatrelvir/ritonavir include:

- **Common (>1%):** Diarrhoea (3.1%), vomiting (1.1%), dysgeusia (altered taste) (5.6%), headache (1.4%)
- **Uncommon (0.1%-1%):** hypertension (0.6%), myalgia (0.6%)
- **Rare (<0.1%):** Hepatic transaminase elevations, clinical hepatitis and jaundice

Refer to the product information for a complete list of possible adverse effects.

Reporting of Adverse Effects:

As Paxlovid® is a TGA 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. Healthcare professionals should report any suspected adverse events to the TGA at http://www.tga.gov.au/reporting-problems .

As Paxlovid® is only available through the National Medical Stockpile, prescribers must complete and submit a **WA Emergency COVID-19 Treatment Approval for nirmatrelvir/ritonavir Form**, for approval for each patient they intend to treat.

This will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines use. The prescribing clinician and any health professional administering nirmatrelvir/ritonavir is responsible for reporting medication errors and adverse events related to nirmatrelvir/ritonavir treatment.

Any clinical incidents related to treatment with nirmatrelvir plus ritonavir (Paxlovid®) that occur within the WA public health system should also be notified into the Datix CIMS and investigated appropriately.

APPENDIX 1: Established and potentially significant interactions with other medicines[1,6]

Paxlovid® is an inhibitor of a number of CYP enzymes (including CYP 3A, 2D6 and 2C9), P-glycoprotein (PGP) and organic anion (OAT) transporters, which may increase plasma concentrations of drugs metabolised by these pathways.

Paxlovid® is also an inducer of a range of CYP enzymes which may reduce plasma concentrations of drugs metabolised by these pathways.

In addition to this, Paxlovid® is itself a substrate of CYP3A, 2D6 and PGP so the concentration of Paxlovid® can be impacted by other medicines that are inhibitors/inducers.

Interactions can be checked using the Liverpool website (link below). These interactions may lead to:

- Clinically significant adverse reactions, including fatal events, from greater exposures of concomitant medications.
- Loss of therapeutic effect of Paxlovid® and possible viral resistance from decreased antiviral exposures.

As a healthcare provider, you should:

- Inform patients that Paxlovid® may interact with medications and is contraindicated for use with some medications.
- Obtain a complete medication list from your patient (including non-prescription drugs and herbals).
- Check for clinically significant drug interactions before prescribing nirmatrelvir/ritonavir (Paxlovid®).

Based on the drug interactions identified, decide if:

- Paxlovid® use is appropriate versus an alternative authorised treatment
- If appropriate, whether your patient should hold, change, or reduce the dose of other medications while taking Paxlovid® or if additional monitoring may be needed.

This list is not meant to be all inclusive. Drug-drug interactions can be checked more completely at Liverpool COVID-19 Drug-Drug Interactions website.

Table 3: Established and potentially significant interactions with other medicines

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Alpha 1-adrenoreceptor antagonist	alfuzosin tamsulosin	↑ alfuzosin ↑ tamsulosin	**Co-administration contraindicated** Hold alfuzosin or tamsulosin during and for 3-5 days post treatment. Risk of significant hypotension.
Analgesics	pethidine, piroxicam	↑ pethidine ↑ piroxicam	**Co-administration contraindicated.** Potential for serious respiratory depression or haematologic abnormalities

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	fentanyl oxycodone morphine tramadol	↑ fentanyl ↑ oxycodone ↑ morphine ↑ tramadol	**Careful monitoring** of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended.
	methadone	↓ methadone	**Careful monitoring** of methadone-maintained patients for evidence of withdrawal effects and dose adjustment. A pre-emptive dose increase is not needed but should be considered in patients reporting symptoms of withdrawal.
Antiarrhythmics	amiodarone, flecainide	↑ antiarrhythmic	**Co-administration contraindicated** due to potential for cardiac arrhythmias. Note the half-life of amiodarone is between 60 to 142 days.
	lidocaine (systemic)	↑ antiarrhythmic	**Careful monitoring** 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 possible resistance
	afatinib	↑ afatinib	**Careful monitoring.** Give afatinib dose before, or at the same time as Paxlovid® dose. Monitor for signs of toxicity.
	neratinib, vinblastine, vincristine	↑ anticancer drug	**Avoid concomitant use where possible**. Co-administration of vincristine or vinblastine may lead to significant haematologic, neurologic, or gastrointestinal side effects.
	abemaciclib, ceritinib, dasatinib ibrutinib, venetoclax	↑ anticancer drug	**Avoid concomitant use where possible.** If unavoidable, refer to relevant Product Information.
	encorafenib	↑ anticancer drug	**Avoid concomitant use where possible.** If unavoidable, reduce dose as follows:

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			450mg to 150mg **300mg, 225mg or 150mg** to 75mg Resume usual dose 3–5 days after completion of Paxlovid® course
	nilotinib	↑ anticancer drug	**Avoid concomitant use where possible.** If unavoidable, reduce dose as follows: For resistant/intolerant CML, 300mg daily For new diagnosis CML in chronic phase, 200mg daily
Anticholinergics	darifenacin, solifenacin	↑ darifenacin ↑ solifenacin	**Careful monitoring.** Reduce dose of darifenacin to 7.5mg daily while taking Paxlovid®. Reduce dose of solifenacin to 5mg daily while taking Paxlovid®.
Anticoagulants	warfarin	↑↓ warfarin	**Careful monitoring** Closely monitor INR if co-administration with warfarin is necessary. Measure INR after 48-72 hours of co-administration and adjust dose; repeat INR 48-72 hours following completion of Paxlovid® course. Moderate increased risk of bleeding.
	rivaroxaban	↑ rivaroxaban	**Co-administration contraindicated.** Increased bleeding risk with rivaroxaban.
	apixaban	↑ apixaban	**Careful monitoring / dose modification** Some product monographs suggest co-administration is possible if the thrombotic risk is low and apixaban dose can be reduced to 2.5mg po BD High increased risk of bleeding.
	dabigatran	↑ dabigatran	**Careful monitoring** Co-administration possible. Monitor clinically for signs of bleeding. Increased risk of bleeding possible.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticonvulsants	carbamazepine, phenobarbital, phenytoin	↓ nirmatrelvir/ritonavir ↑ carbamazepine ↓ phenobarbital ↓ phenytoin	**Co-administration contraindicated** due to potential loss of virologic response and possible resistance
	lamotrigine	↓ lamotrigine	**Careful monitoring** of serum levels or therapeutic effects is recommended when these medicines are co-administered with Paxlovid®.
Antidepressants	amitriptyline, fluoxetine, imipramine, mirtazapine, nortriptyline, paroxetine	↑ amitriptyline ↑ fluoxetine ↑ imipramine ↑ mirtazapine ↑ nortriptyline ↑ paroxetine	**Careful monitoring** of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir.
Antifungals	voriconazole	↑↓ voriconazole ↑ nirmatrelvir plus ritonavir	**Co-administration contraindicated**
	ketoconazole, itraconazole	↑ ketoconazole ↑ itraconazole ↑ nirmatrelvir plus ritonavir	**Avoid concomitant use where possible.** Refer to relevant Product Information.
	isavuconazole	↑ isavuconazole ↓ nirmatrelvir plus ritonavir	**Co-administration contraindicated** due to potential loss of virologic response and possible resistance
Anti-gout	colchicine	↑ colchicine	**Co-administration contraindicated**. Potential for serious and/or life-threatening reactions. Hold colchicine during and for 3-5 days after treatment. If colchicine cannot be held do not use Paxlovid®. Risk of fatal colchicine toxicity.
Anti-HIV protease inhibitors	atazanavir, darunavir, fosamprenavir, saquinavir, tiprinavir	↑ atazanavir ↑ darunavir ↑↓ fosamprenavir ↑ saquinavir ↑ tipranavir	**Careful monitoring** for therapeutic and adverse effects required. Refer to relevant Product Information. Patients on ritonavir-containing HIV regimens should continue their treatment as indicated. Monitor for increased Paxlovid® or protease inhibitor adverse events.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anti-HIV	Efavirenz	↑ efavirenz	**Avoid concomitant use where possible**. Combination is not well tolerated due to increased adverse effects.
	maraviroc, nevirapine, raltegravir, zidovudine, bictegravir, tenofovir	↑ maraviroc ↑ nevirapine ↓ raltegravir ↓ zidovudine ↑ bictegravir ↑ tenofovir	Interaction unlikely to be clinically significant. Refer to relevant Product Information.
Antihistamine	loratadine	↑loratadine	Interaction unlikely to be clinically significant. Refer to relevant Product Information.
Antihyperglycaemics	saxagliptin	↑ saxagliptin	**Careful monitoring.** Reduce dose to 2.5mg daily while taking Paxlovid®**.**
Anti-infective	clarithromycin, erythromycin	↑ clarithromycin ↑ erythromycin	**Avoid concomitant use where possible.** Consider use of alternative agent or refer to relevant Product Information.
	atovaquone	↓ atovaquone	**Avoid concomitant use where possible**. If unavoidable monitor for loss of atovaquone effects.
Antimigraine	eletriptan	↑ eletriptan	**Do not give eletriptan within 72 hours of Paxlovid®.**
Antimycobacterial	rifampicin	↓ nirmatrelvir/ritonavir	**Co-administration contraindicated** due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as rifabutin should be considered.
	rifabutin	↑ rifabutin	**Careful monitoring.** Reduce rifabutin dose to 150mg on alternate days or 150mg on 3 days each week. Refer to relevant product Information. *(As per Up to Date – Lexicomp Drug Interaction Checker)*
Antiplatelets	clopidogrel, ticagrelor,	↓ clopidogrel active metabolites ↑ ticagrelor	**Co-administration contraindicated.** Consider use of prasugrel. Use an alternative COVID-19 treatment where available.
Antipsychotics	lurasidone, clozapine	↑ lurasidone ↑ clozapine	**Co-administration contraindicated** due to serious and/or life-threatening reactions such as cardiac arrhythmias.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	quetiapine	↑ quetiapine	**Avoid concomitant use where possible.** If unavoidable reduce dose to one sixth of original dose during and for 3-5 days after completion of Paxlovid® course. High risk of sedation. Consider ECG monitoring.
	haloperidol, risperidone	↑ haloperidol ↑ risperidone	**Careful monitoring** for therapeutic and adverse effects required. Refer to relevant Product Information.
Calcium channel blockers	amlodipine, diltiazem, felodipine, nifedipine	↑ calcium channel blocker	**Careful monitoring** for therapeutic and adverse effects required. Dose reduction may be warranted during and for 3-5 days after completion of Paxlovid® course, refer to relevant Product Information.
Cardiac glycosides	digoxin	↑ digoxin	**Careful monitoring** for therapeutic and adverse effects required. Measure digoxin level after 48-72 hours of co-administration and adjust dose based on patient factors.
Endothelin receptor Antagonists	bosentan	↑ bosentan	**Co-administration contraindicated.** Hold bosentan ≥36 hours before starting and for 3-5 days after completing Paxlovid® course.
	riociguat	↑ riociguat	**Avoid concomitant use where possible.** If unavoidable, refer to relevant Product Information.
Ergot derivatives	ergometrine	↑ ergometrine	**Co-administration is contraindicated.**
Hepatitis C direct acting antivirals	Glecaprevir plus pibrentasvir	↑ antiviral	**Co-administration contraindicated.**
	Sofosbuvir plus velpatasvir plus voxilaprevir	↑ antiviral	**Avoid concomitant use where possible.** Patients on ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased Paxlovid® or HCV drug adverse events. Monitor LFTs.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Herbal products	St. John's Wort (*Hypericum perforatum*)	↓ nirmatrelvir/ ritonavir	**Co-administration contraindicated** due to potential loss of virologic response and possible resistance.
	Garlic supplements	↓ ritonavir	**Co-administration contraindicated** due to potential loss of virologic response and possible resistance.
HMG-CoA reductase inhibitors	simvastatin	↑ simvastatin	**Co-administration contraindicated**. Hold simvastatin ≥ 12 hours before starting and for 3-5 days after completing Paxlovid® course, or change to a low-potency statin such as pravastatin.
	atorvastatin, rosuvastatin	↑ atorvastatin ↑ rosuvastatin	**Co-administration contraindicated**. Hold statin during and for 3-5 days after completing Paxlovid® course, or change to a low potency statin such as pravastatin.
Hormonal contraceptive	ethinylestradiol	↓ ethinylestradiol	Interaction unlikely to be clinically significant, however an additional, non-hormonal method of contraception is strongly recommended during and for 3-5 days after completing Paxlovid® course.
Immunosuppressants	everolimus	↑ everolimus	**Co-administration contraindicated** unless close TDM available every 2-4 days during and for ≥ 2 weeks after completing Paxlovid® course. Seek specialist advice for immunosuppressant therapy in combination with Paxlovid®. Use an alternative COVID-19 treatment where available.
	ciclosporin, tacrolimus, sirolimus,	↑ ciclosporin ↑ tacrolimus ↑ sirolimus	**Co-administration contraindicated.** Use an alternative COVID-19 treatment or seek specialist advice for interruption of immunosuppressant therapy.
Long-acting beta-adrenoceptor agonist	salmeterol	↑ salmeterol	**Co-administration contraindicated** due to

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			increased risk of cardiovascular adverse events including QT prolongation, palpitations, and sinus tachycardia.
PDE5 inhibitor	Sildenafil, avanafil, tadalafil, vardenafil	↑ sildenafil ↑ avanafil ↑ tadalafil ↑ vardenafil	**Co-administration contraindicated** due to increased risk of adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope.
Sedative/hypnotics	midazolam (administered parenterally)	↑ midazolam	**Careful monitoring** in a setting which ensures close clinical monitoring and appropriate medical management required during and for 3-5 days after completion of Paxlovid® course. Dose reduction should be considered, especially if more than a single dose is administered. Risk of extreme sedation and respiratory depression.
	diazepam clonazepam	↑ diazepam ↑ clonazepam	**Co-administration contraindicated** Risk of extreme sedation and respiratory depression. Hold diazepam or clonazepam during and for 3-5 days after completion of Paxlovid® course.
	alprazolam	↑ alprazolam	**Avoid concomitant use where possible.** Risk of over-sedation and respiratory depression during and for 3-5 days after completion of Paxlovid® course.
Sleeping agent	zolpidem	↑ zolpidem	**Careful 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, prednisone	↑ corticosteroid	**Careful monitoring** for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone and prednisolone should be considered.

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
	methyl-prednisolone, triamcinolone	↑ corticosteroid	**Avoid concomitant use where possible.** Alternative corticosteroids including beclomethasone and prednisolone should be considered.

- Nirmatrelvir + ritonavir (Paxlovid®) is an inhibitor of CYP3A and may increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A.
- Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following ranked order: CYP3A4 > CYP2D6 > CYP2C9, CYP2C19 >> CYP2A6, CYP1A2, CYP2E1.
- Ritonavir also has a high affinity for P-glycoprotein (P-gp) and may inhibit this transporter. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19. This increases the biotransformation of some medicinal products metabolised by these pathways and may result in decreased systemic exposure to such medicinal products. This could decease or shorten their therapeutic effect.
- Co-administration of other CYP3A4 substrates that may lead to potentially significant drug interactions should be considered only if the benefits outweigh the risks.

References:

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5. National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. https://covid19evidence.net.au/#living-guidelines . Version 50.1 published 3 February 2022. Accessed 7 February 2022
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Version Control

Version	Date	Comments
1.0	7/2/2022	Compiled Guideline
2.0	25/2/2022	Endorsed by COVID-19 EAG
3.0	9/5/2022	PBS listing update, 12-18 year old over 40 kg NCCET recommendation

This guidance is correct at the time of publishing. However, as it is subject to updates, please use the hyperlinks to confirm the information is accurate.

WA guidance may be amended as additional federal guidance is finalised and/or further information becomes available.