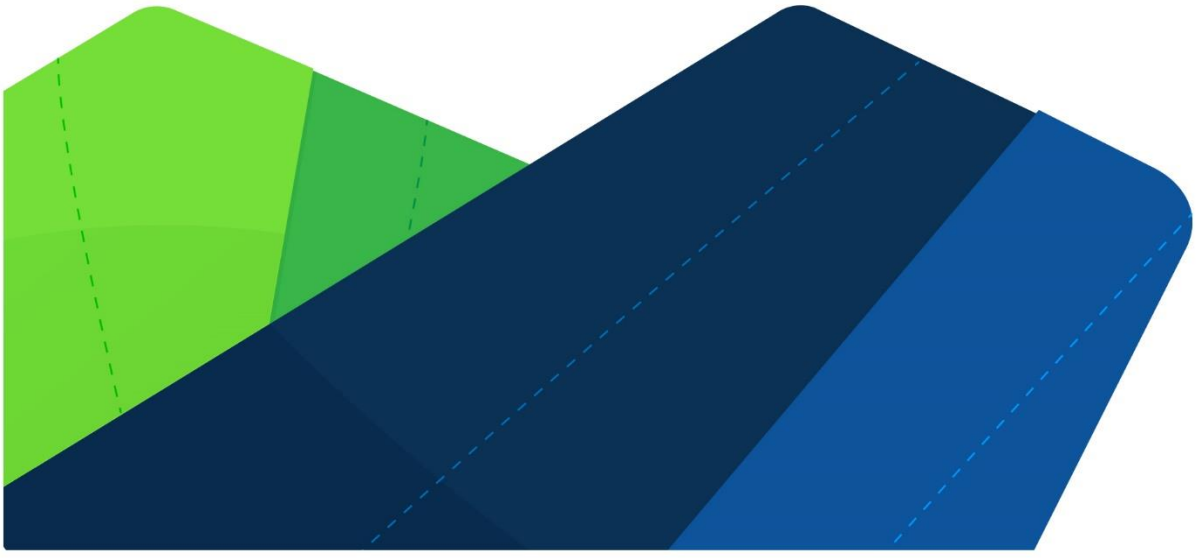
Nirmatrelvir plus ritonavir prescribing guideline

Department of Health

April 2022



Queensland Government

Nirmatrelvir plus ritonavir prescribing guideline

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An electronic version of this document is available at: https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/novel-coronavirus-qld-clinicians

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1. Purpose

This guideline has been developed by the Queensland Health COVID-19 Therapeutics Working Group to provide clinicians with information and guidance around the appropriate prescribing and safe administration of nirmatrelvir plus ritonavir (Paxlovid®) in patients diagnosed with COVID-19, and to ensure equity of access to new COVID-19 therapeutics. This guideline requires endorsement by local Drugs and Therapeutics Committees or equivalent before implementation.

2. Background

This guideline and procedure are based on the findings of the EPIC-HR trial[1] and the recommendations of the National COVID-19 Clinical Evidence Taskforce (NCCET). These guidelines will be updated as data are made available.

2.1 Regulatory status

Nirmatrelvir plus ritonavir has been granted provisional approval by the Therapeutic Goods Administration (TGA). Approval has been made based on short-term efficacy and safety data. Continued approval depends on evidence from ongoing clinical trials and post-market assessment. The product is subject to additional monitoring in Australia.

2.2 Mechanism of action

This treatment uses nirmatrelvir and ritonavir in combination. Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease, including the SARS-CoV-2 3CL protease. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication[2].

Nirmatrelvir is administered in combination with low-dose ritonavir (which inhibits the CYP3A-mediated metabolism of nirmatrelvir) to maintain adequate plasma levels of nirmatrelvir.

2.3 Efficacy

The data supporting nirmatrelvir plus ritonavir primarily comes from an interim analysis of the EPIC-HR trial[1]. This study included participants 18 years of age and older with at least 1 of the following risk factors for progression to severe disease: diabetes, being overweight (BMI > 25kg/m^2), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, diabetes, sickle cell disease, neurodevelopmental disorders, active cancer or medically-related technological dependence, or were 60 years of age and older regardless of comorbidities. The study excluded individuals with a known history of COVID-

19 infection or vaccination. Participants with COVID-19 symptom onset of ≤ 5 days were included in the study.

At the primary completion date, there were 697 participants in the nirmatrelvir plus ritonavir group and 682 participants in the placebo group. The event rate of a COVID-19-related hospitalisation or death from any cause (reported until Day 28) in participants who received treatment within 3 days of symptom onset was 44/682 (6.45%) in the placebo group, and 5/697 (0.72%) in the nirmatrelvir plus ritonavir group. This represents an absolute risk reduction of 5.81% (95% CI: -7.78% to -3.84; p<0.0001), or an 88.9% relative reduction in primary endpoint events compared to placebo. No deaths were reported in the nirmatrelvir plus ritonavir group compared with 9 deaths in the placebo group.

3. Prescription and governance

Nirmatrelvir plus ritonavir has a restricted listing on the Queensland Health Medicines Formulary (List of Approved Medicines): *on the advice of an Infectious Diseases physician for the treatment of COVID-19 in accordance with recommendations in the Statewide COVID-19 Treatment Guidelines and Nirmatrelvir plus ritonavir Prescribing Guidelines*

Individual governance of nirmatrelvir plus ritonavir prescribing should be managed by a lead clinician in each Hospital and Health Service.

3.1 Authorised prescribers

Patients should be assessed by their treating clinician, with suitable patients then discussed with the on-call adult Infectious Diseases physician or approved delegate for your service.

Prescribers are to complete a Request to Access Form for each patient, confirming patient suitability and consent to treatment.

3.2 Patient consent

There are no additional requirements for consent to administer nirmatrelvir plus ritonavir than is usual practice for any other TGA registered pharmaceutical. Clinicians should discuss the risks and benefits of treatment with the patient and/or their carer and document that this has been done in the patient record. A patient information leaflet has been developed to assist with this and should be provided to the patient. Some clinicians may wish to obtain formal written consent and a consent form has been developed for this purpose.

4. Access and supply

Access to nirmatrelvir plus ritonavir is regulated by the National Medical Stockpile and managed centrally in Queensland by Central Pharmacy. Supply of COVID-19 therapeutics including nirmatrelvir plus ritonavir is uncertain and vulnerable to constraints in the supply chain as demand fluctuates nationally and globally. To ensure equity of access and conserve this agent for those patients at the highest risk of disease progression, an expert group of lead clinicians from across the medical specialties has identified priority groups for treatment — see the COVID-19 Treatment Guidelines for mild to moderate disease (Adult).

Access will be closely monitored, and prescribers will be required to complete a Request to Access Nirmatrelvir plus ritonavir form for each patient – available online.

5. Clinical criteria for treatment

5.1 Contraindications

Due to significant drug interactions, every patient requires a complete medication history (including prescribed and nonprescribed medications) to be taken and a drug interaction check before administration of nirmatrelvir plus ritonavir. Drug interactions should be checked in the COVID-19 drug interactions checker provided by the University of Liverpool – if the medication is not listed in this interaction checker, see section 5.2 below for alternative ways to check for drug interactions.

Nirmatrelvir is contraindicated in:

- patients with a history of clinically significant hypersensitivity reactions to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product (list of excipients provided below)
- severe renal impairment (eGFR < 30 mL/min/1.73m^2) including patients on dialysis.
- severe hepatic impairment (Child-Pugh Class C)
- patients concurrently taking drugs listed in Table 1 (many other drug interactions may also preclude the use of nirmatrelvir plus ritonavir)
- patients who are pregnant or breastfeeding
- people with a HIV viral load of >400 copies per mL.

Table 1. Drugs contraindicated with concurrent use of nirmatrelvir plus ritonavir.

Class	Drug	Management
Prostate gland enlargement	alfuzosin	If possible, withhold alfuzosin during and for 3 days after the nirmatrelvir plus ritonavir course, if not possible do not use nirmatrelvir plus ritonavir.
Antiarrhythmics	amiodarone, flecainide, disopyramide, quinidine	Do not use nirmatrelvir plus ritonavir.
Cancer chemotherapy	neratinib, veneoclax, apalutamide	Do not use nirmatrelvir plus ritonavir.
Anti-gout medications	colchicine	If possible, withhold colchicine during and for 3 days after the nirmatrelvir plus ritonavir course, if not possible do not use nirmatrelvir plus ritonavir*.
Antipsychotics	lurasidone, clozapine, quetiapine	Do not use nirmatrelvir plus ritonavir.
Ergot derivatives	ergometrine, dihydroergotamine	Do not use nirmatrelvir plus ritonavir.
HMG-CoA reductase inhibitors	lovastatin, simvastatin, high-dose atorvastatin, high-dose rosuvastatin	If possible, withhold the statin or (for atorvastatin or rosuvastatin) reduce the dose (per the Uni of Liverpool drug interaction checker recommendation for max dose), during and for 3 days after nirmatrelvir plus ritonavir course, if not possible do not use nirmatrelvir plus ritonavir.
Analgesics	pethidine, piroxicam, dextropropoxyphene (other opioids may need dose reduction or monitoring for toxicity)	Do not use nirmatrelvir plus ritonavir.
PDE5 inhibitors	avanafil, sildenafil, vardenafil, tadalafil	For erectile dysfunction or Raynaud phenomenon: withhold PDE5 inhibitor during and for 3 days after nirmatrelvir plus ritonavir For pulmonary hypertension, pulmonary oedema: do not use nirmatrelvir plus ritonavir.
Benzodiazepines	clonazepam, diazepam, midazolam	If possible, withhold the benzodiazepine (consider risk of withdrawal) or switch to an alternative that does not interact (eg temazepam, lorazepam) during and for 3 days after the nirmatrelvir plus ritonavir course, if not possible, do not use nirmatrelvir plus ritonavir.
Antimicrobials	rifampicin, rifapentine, fusidic acid	Do not use nirmatrelvir plus ritonavir.

Anticoagulants or antiplatelets	apixaban, dabigatran, clopidogrel, rivaroxaban, ticagrelor.	Do not use nirmatrelvir plus ritonavir.
Anticonvulsants	carbamazepine, phenobarbital, phenytoin, primidone	Do not use nirmatrelvir plus ritonavir.
Antidepressants	St John's wort	Do not use nirmatrelvir plus ritonavir.
Bronchodilators	salmeterol	Withhold salmeterol or switch to an alternative beta$_2$ agonist if unable to withhold.
Gastrointestinal drugs	cisapride, domperidone	If possible, withhold these drugs during and for 3 days after nirmatrelvir plus ritonavir course, if not possible do not use nirmatrelvir plus ritonavir.
Hepatitis C antivirals	elbasavir/grazoprevir, glecaprevir/pribrentasvir	Do not use nirmatrelvir plus ritonavir.
Cardiac drugs	ranolazine, bosenten, eplerenone, ivabradine, lercanidipine	Do not use nirmatrelvir plus ritonavir.
Immunosuppressants	ciclosporin, tacrolimus, everolimus, sirolimus	Can be used concurrently with specialised monitoring and drug dose adjustments. Concurrent use requires transplant specialist involvement and drug concentration monitoring. If not available, do not use nirmatrelvir plus ritonavir.
*Monitor for colchicine toxicity in patients with kidney or liver impairment. **Many other medications interact with nirmatrelvir plus ritonavir and may mean nirmatrelvir plus ritonavir is relatively contraindicated.** **Every medication the patient is taking must be checked in the COVID-19 drug interaction checker—available from:** www.covid19-druginteractions.org/checker.		

List of excipients for Paxlovid®: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, sodium stearylfumarate, copovidone, calcium hydrogen phosphate, sorbitan monolaurate, hypromellose, titanium dioxide, macrogol 400, hyprolose, purified talc, macrogol 3350m polysorbate 80, coating System 05B140011 Pink.

5.2 Precautions and drug interactions

Due to significant drug interactions, every patient requires a complete medication history (prescribed and nonprescribed medications) to be taken and drug interaction check before administration of nirmatrelvir plus ritonavir. Drug interactions should be checked in the COVID-19 drug interactions checker provided by the University of Liverpool. Drug interactions relate to use of ritonavir, which inhibits CYP enzymes (in ranked order CYP3A4 > CYP2D6 > CYP2C9, CYP2C19 >> CYP2A6, CYP1A2, CYP2E1) and P-glycoprotein[2]. Ritonavir can also induce CYP1A2, CYP2C8, CYP2C9 and CYP2C19[2]. If the patient's regular medication is not listed in the University of Liverpool drug interactions checker, try using Micromedex or Lexicom (via Up To Date—if available), look for published cases or use the available product information to determine likelihood of interaction based on metabolism involving enzymes above. Feed back to the University of Liverpool website (pop up on bottom right-hand corner) the drug that was not available so it can be added.

Many medications are not contraindicated but require alteration (eg temporarily pausing administration, dose adjustment, monitoring of plasma concentrations) to safely facilitate nirmatrelvir plus ritonavir therapy.

Despite the short duration of therapy of nirmatrelvir plus ritonavir, drug interactions can still occur as maximal inhibition of CYP3A4 enzymes occurs within approximately 48 hours of starting ritonavir. CYP3A4 inhibition also persists after stopping ritonavir, with inhibition resolving 3 days after stopping therapy in most young and elderly individuals, though there is inter-individual variability.

In general, medications that have been stopped can be restarted 3 to 5 days after the nirmatrelvir plus ritonavir course is complete. Similarly, if a dose adjustment has been made, drugs can go back the original dose 3 to 5 days after the nirmatrelvir plus ritonavir course is complete. Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.

Patients taking combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with, and until one menstrual cycle after stopping nirmatrelvir plus ritonavir.

Patients with HIV who are not being treated with antiretroviral therapy: because nirmatrelvir is co-administered with ritonavir, there may be a risk of developing resistance to HIV protease inhibitors in individuals with untreated or undiagnosed HIV-1 infection. Nirmatrelvir plus ritonavir is contraindicated in people with a HIV viral load of >400 copies per mL.

Patients with pre-existing liver disease: serum aminotransferase elevation has occurred with ritonavir when it has been used in combination therapy for HIV treatment—advise patients to avoid concurrent hepatotoxins (eg alcohol).

5.3 Indications

Before prescribing check for drug interactions and other contraindications (see section 5.2 and 5.3)

Nirmatrelvir plus ritonavir can be used for patients with:

- SARS-CoV-2 infection confirmed by either
  - Polymerase chain reaction (PCR) testing OR
  - Rapid antigen test (RAT)

AND

- Symptomatic (mild to moderate) with COVID-19 (within 5 days of symptom onset)

AND

- Patient meets criteria for therapy:
  - Per vaccination status as outlined in table 2

    OR
  - Immunosuppressed regardless of vaccination status (refer to appendix 1)

Table 2. Eligibility based on vaccination status

Patient group ***this does not apply to immunosuppressed patients**	**Eligible for therapy**
• Age ≥ 70 or ≥ 55 if Aboriginal or Torres Strait Islander • Age ≥ 55 (or ≥ 35 if Aboriginal or Torres Strait Islander) **with ONE or more additional risk factors** for severe disease (i.e., aside from age or Indigenous status)	If have not completed a schedule of BOTH: • 2 dose^ primary course and • a booster¥ (i.e.: not eligible if double vaccinated and boosted)
• Age ≥ 55 (or ≥ 35 if Aboriginal or Torres Strait Islander) **with NO additional risk factors** for severe disease • Age < 55 (or < 35 if Aboriginal or Torres Strait Islander) **with ANY risk factor** for severe disease	If have not completed: • 2 dose^ primary course OR • < 2 weeks since 2nd dose (i.e.: not eligible if double vaccinated)

Risk factors for severe disease:

- Diabetes mellitus (requiring medication)
- Obesity (BMI > 30 kg/m^2)
- Chronic kidney disease (i.e., eGFR <60 mL/min/1.73m^2)
- Serious cardiac conditions (such as heart failure, coronary artery disease or cardiomyopathy)
- Pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, significant bronchiectasis or emphysema with dyspnoea on physical exertion)
- Moderate to severe asthma (requiring an inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months)
- Age ≥ 55 years or age > 35 years if Aboriginal or Torres Strait Islander
- Other significant risk factors:
    - Medical related technologic dependence (CPAP, other ventilation not related to COVID-19)
    - Neurodevelopment disorders (eg cerebral palsy, Down's syndrome)
    - Sickle cell disease
    - Neuromuscular disease with respiratory involvement (spinal cord injury, post-polio syndrome, spinal muscular atrophy, motor neurone disease, Duchenne or other muscular dystrophy, myasthenia gravis)

5.4 Fertility, Pregnancy and Breastfeeding

There are no human data on the effect of nirmatrelvir plus ritonavir on fertility. In animal studies, no effect of nirmatrelvir or ritonavir has been seen on fertility, even at very high doses.

Use in pregnancy – Category B3.

Nirmatrelvir plus ritonavir is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

There are no human data on during pregnancy to evaluate the drug-associated risk of adverse developmental outcomes; women of childbearing potential should avoid becoming pregnant during treatment and until after 7 days after stopping nirmatrelvir plus ritonavir.

There are 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. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breast-fed newborn/infant or the effects of the medicinal product on milk production. Current advice is to discontinue. Breastfeeding should be discontinued during treatment with nirmatrelvir plus ritonavir and for 7 days after the last dose.

5.5 Use in children

The safety and efficacy of nirmatrelvir plus ritonavir in paediatric patients younger than 18 years of age have not yet been established. No data are available.

6. Prescribing and administration

6.1 Dose and duration

Nirmatrelvir must be taken at the same time as ritonavir, with or without food. Failure to correctly co-administer nirmatrelvir with ritonavir may result in plasma levels of nirmatrelvir that are insufficient to achieve the desired therapeutic effect. Paxlovid® is supplied as pink 150 mg nirmatrelvir tablets and white 100mg ritonavir tablets.

Nirmatrelvir plus ritonavir dosing is based on renal function:

- eGFR > 60 ml/min: 300 mg nirmatrelvir (2 pink tablets) plus 100 mg ritonavir (1 white tablet) orally, 12-hourly for 5 days (total: 3 tablets twice day)
- eGFR ≤ 60 and ≥ 30 mL/min: 150 mg nirmatrelvir (1 pink tablet) plus 100 mg ritonavir (1 white tablet) orally, 12-hourly for 5 days (total: 2 tablets twice a day)
- eGFR <30 mL/min: not recommended.

For patients with renal impairment needing dose reduction – amendments to the nirmatrelvir plus ritonavir packaging is required. See the patient safety communique, available here.

Do not crush the tablet. There is no information on the effect of crushing the medication will have on drug exposure. Absorption of ritonavir is decreased when the combination tablet (with lopinavir) is crushed[3].

If a patient misses a dose, advice on what to do is based on how long it has been since the usual dose administration time. If it has been less than 8 hours since they were meant to take the dose, advise the patient to take the tablet immediately. If it has been longer than 8 hours since they were meant to take the dose, the patient can skip the missed dose and take the next dose at scheduled time. Patients should not take a double dose to make up for any missed doses.

Examples of how to prescribe are provided in Appendix 2, below.

6.2 Presentation, storage and stability

PAVLOVID®: nirmatrelvir is supplied as oval, pink immediate-release, film-coated tablets debossed with “PFE” on one side and “3CL” on the other side. Each tablet contains 150 mg of nirmatrelvir. Ritonavir is supplied as white film-coated ovaloid tablets debossed with the "a" logo and the code NK. Each tablet contains 100 mg of ritonavir.

PAVLOVID® is supplied in a carton of 30 tablets in five blister cards marked as “Morning Dose” and “Evening Dose” for tablets to be taken each morning and each evening. Each blister card contains four nirmatrelvir tablets and two ritonavir tablets.

Store tablets below 25°C.

6.3 Adverse effects and reporting

The safety of nirmatrelvir plus ritonavir is based on data from EPIC-HR, a Phase 2/3 randomised, placebo-controlled trial in 2,224 non-hospitalised adult participants with COVID-19. Adverse events were those reported while subjects were on study medication and through Day 34 after initiating study treatment. nirmatrelvir plus ritonavir or placebo were to be taken twice daily for 5 days.

The reported adverse events reported during treatment with nirmatrelvir plus ritonavir this study were:

- dysgeusia
- diarrhoea
- headache
- vomiting
- hypertension

- myalgia.

The proportions of subjects who discontinued treatment due to an adverse event were 23 (2.1%) in the nirmatrelvir plus ritonavir group and 47 (4.2%) in the placebo group. The proportion of subjects with serious adverse events were 18 (1.6%) and 74 (6.6%) in the nirmatrelvir plus ritonavir group and in the placebo group, respectively.

However, because nirmatrelvir plus ritonavir is a provisionally approved product with no post-marketing data, all possible and confirmed adverse events must be reported. These should be notified to the TGA Reporting adverse events | Therapeutic Goods Administration (TGA) and reported via Riskman.

6.4 Monitoring of treatment outcomes

The use of nirmatrelvir plus ritonavir requires reporting of clinical outcomes to the National Medical Stockpile Taskforce. Prescribers agree to these terms when completing a Request to access form. Data required includes eligibility, confirmation of full dose delivery and outcome: recovery, progression to hospitalisation, oxygen requirement, ICU or death.

7. Vaccination after nirmatrelvir plus ritonavir

Suitability for ongoing vaccination is related to the patient's recovery from COVID-19 and is not influenced by receipt of nirmatrelvir plus ritonavir.

8. Compliance and evaluation

Regular prescribing reports will be provided through interrogation of iPharmacy, ieMR and CHARM programs. Reports will be made available to Medication and Pharmacy Planning Response Group (MPPRG).

9. References:

1. Hammond J, Leister-Tebbe H, Gardener A *et al*. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. New England Journal of Medicine. 2022; DOI: 10.1056/NEJMoa2118542
2. Pfizer (Australia) Pty Ltd. Australian product information – Paxlovid® (nirmatrelvir+ritonavir) capsules. Published March 1, 2022.
3. Society of Hospital Pharmacists of Australia. 2022, Don't rush to crush, 4th edn. Melbourne. Vic.

Appendix 1: Priority groups for treatment

	ELIGIBLE PATIENTS[1]	PRIORITY GROUPS
Patients who are not up to date with vaccination (per table 2)	**With a moderate risk factor:** • Age ≥ 55 (or > 35 if Aboriginal and Torres Strait Islander) • Obesity (BMI ≥ 30 kg/m^2) • Chronic kidney disease (eGFR < 60 mL/min/1.73m^2, dose reduce if eGFR <60mL/min/1.73m^2, contraindicated if eGFR <30mL/min/1.73m^2) • Serious cardiac condition (such as heart failure, coronary artery disease or cardiomyopathy) • Pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, significant bronchiectasis or emphysema with dyspnoea on physical exertion) • Moderate-to-severe asthma (requiring inhaled steroid as a preventor) or prescribed a course of oral steroids in the previous 12 months • Diabetes mellitus (type 1 or 2 requiring medication) • Medical related technologic dependence (CPAP, other ventilation not related to COVID-19) • Neurodevelopment disorders (including cerebral palsy, Down's syndrome etc) • Sickle cell disease • Patients with neuromuscular disease with respiratory muscle involvement (spinal cord injury, post-polio syndrome, spinal muscular atrophy, motor neurone disease, Duchenne or other muscular dystrophy, myotonic dystrophy, myasthenia gravis)	**High risk patients:** • All patients aged ≥ 70 years or ≥55 years if Aboriginal or Torres Strait Islander • Age > 55 years **with** an additional COVID risk factor (obesity (BMI > 30kg/m^2), diabetes (requiring medication), CKD with eGFR <60 mL/min/1.73m^2 but >30 mL/min/1.73m^2, heart failure) **OR** significant underlying bronchiectasis • Age > 35 years and Aboriginal and Torres Strait Islander **with** an additional COVID risk factor (obesity (>30kg/m^2), diabetes (requiring medication), CKD with eGFR <60 mL/min/1.73m^2 but >30 mL/min/1.73m^2, heart failure) **OR** significant underlying bronchiectasis
REGARDLESS OF VACCINATION STATUS		
Patients on immunosuppressive therapy: Biologic agents / TKIs / cellular therapies (irrespective of vaccination status)	• Rituximab / obintuzumab / BITE antibodies within 12 months • CAR-T within 24 months • Alemtuzumab within 6 months • Ibrutinib, acalabrutinib, venetoclax within 6 months • Daratumumab within 6 months • Ruxolitinib within 6 months • JAK inhibitors: baricitinib, tofacitinb, upadacitinib	• Rituximab / obintuzumab / BITE antibodies within 6 months • CAR-T within 12 months • Alemtuzumab within 3 months

	ELIGIBLE PATIENTS[1]	PRIORITY GROUPS
	• Bortezomib / carfilzomib • Lenalidomide / pomalidomide • TKIs and other targeted therapies (dasatinib, nilotinib, imatinib, osimertinib, erlotinib, crizotinib, alectinib, lorlatinib, etc) • Complement inhibitors (eculizumab) • Anti-TNF (infliximab, adalimumab, etanercept, golimumab, certolizumab) or Anti-IL-6 (tocilizumab) when used in combination with other DMARDs • S1PR modulators (fingolimod, siponimod) • Belimumab	
Other immunosuppressive therapy: Corticosteroids / DMARDs (irrespective of vaccination status)	• Mycophenolate • Azathioprine (≥ 1 mg/kg/day) • Mercaptopurine (≥ 0.5 mg/kg/day) • Methotrexate (≥ 10mg/week) • Prednisone ≥ 20mg /day (or equivalent) for ≥ two weeks • Abatacept • Dapsone • Leflunomide > 10mg/day • Calcineurin inhibitors (cyclosporin, tacrolimus) • mTOR inhibitors (sirolimus, everolimus)	• Prednisone ≥ 20mg day (or equivalent) for > 4 weeks • Combination therapy with corticosteroids and x 2 DMARDs
Transplantation (irrespective of vaccination status)	• Autologous stem cell transplantation within 12 months • Solid organ transplantation on immunosuppression • Allogeneic stem cell transplantation within 2 years or on immunosuppression / chronic GVHD	• Autologous stem cell transplantation within 6 months • Solid organ transplantation on immunosuppression • Allogeneic stem cell transplant within 2 years or on immunosuppression / chronic GVHD

	ELIGIBLE PATIENTS[1]	PRIORITY GROUPS
Chemotherapy / malignancy (irrespective of vaccination status)	• Acute myeloid leukaemia induction / consolidation within 6 months • Acute lymphoblastic leukaemia induction / consolidation / maintenance within 12 months • Lung cancer on active chemotherapy +/- immunotherapy within 6 months • Other malignancies (both haematological and solid cancer): moderate intensity chemotherapy within 2 weeks (defined as high risk of severe neutropenia (neutrophils <0.5 x 10^9/L) for 3-5 days duration post-chemotherapy) • Recent whole body radiotherapy or total lymphoid irradiation	• Acute myeloid leukaemia induction / consolidation within 3 months • Acute lymphoblastic leukaemia induction / consolidation / maintenance within 6 months • Lung cancer on active chemotherapy +/- immunotherapy within 3 months • Other malignancies (both haematological and solid cancer): moderate intensity chemotherapy within 2 weeks (as defined by high risk of severe neutropenia (neutrophils <0.5 x 10^9/L) for 3-5 days duration post-chemotherapy) • High dose cyclophosphamide (>1 g/m^2) within 2 weeks
Immunodeficiency disorders (irrespective of vaccination status)	• Major antibody deficiency (i.e CVID or XLA) • Combined immunodeficiency syndromes including transplanted SCID where immunoglobulin replacement is required. • HIV infection with CD4 <250 cells/mm^3 • Aplastic anaemia on active therapy • Primary immunodeficiency syndromes where immunoglobulin replacement is required (excluding specific antibody deficiency) • Secondary hypogammaglobulinemia requiring immunoglobulin replacement – risk related to underlying therapy / disease resulting in 2nd hypogammaglobulinemia	• Major antibody deficiency (i.e CVID or XLA) with an additional COVID risk factor (age > 55 years, obesity (BMI >30kg/m^2), diabetes (requiring medication), CKD (eGFR <60mL/min/1.73m^2 but >30 mL/min/1.73m^2), heart failure) **OR** significant underlying bronchiectasis **OR** on immunosuppressive therapy • Combined immunodeficiency syndromes including transplanted SCID where immunoglobulin replacement is required • HIV infection with CD4 <250 cells/mm^3 • Aplastic anaemia on active therapy

1. Nirmatrelvir is contraindicated in patients with an eGFR < 30 mL/min/1.73m^2, severe hepatic impairment (Child-Pugh Class C), patients who are pregnant or breastfeeding, those with a HIV viral load >400 copies/mL, and in those with clinically significant drug interactions.

Appendix 2: Prescribing examples

Image 1. Prescribing on the National Standard Medication Chart for patients without renal impairment (change the dose for those with eGFR < 60mL/min/1.73m^2 but > 30mL/min/1.73m^2).

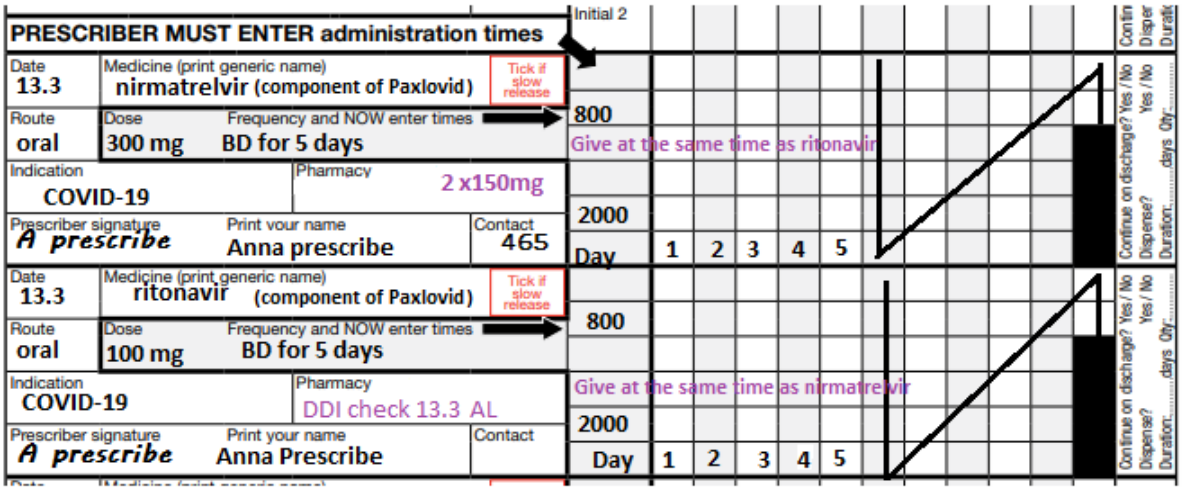


Image 2. Non-inpatient prescription for nirmatrelvir plus ritonavir or patients without renal impairment (change the dose and quantity for those with eGFR < 60mL/min/1.73m^2 but > 30mL/min/1.73m^2, information on how to amend the packs is available here—accessible via QH intranet only).

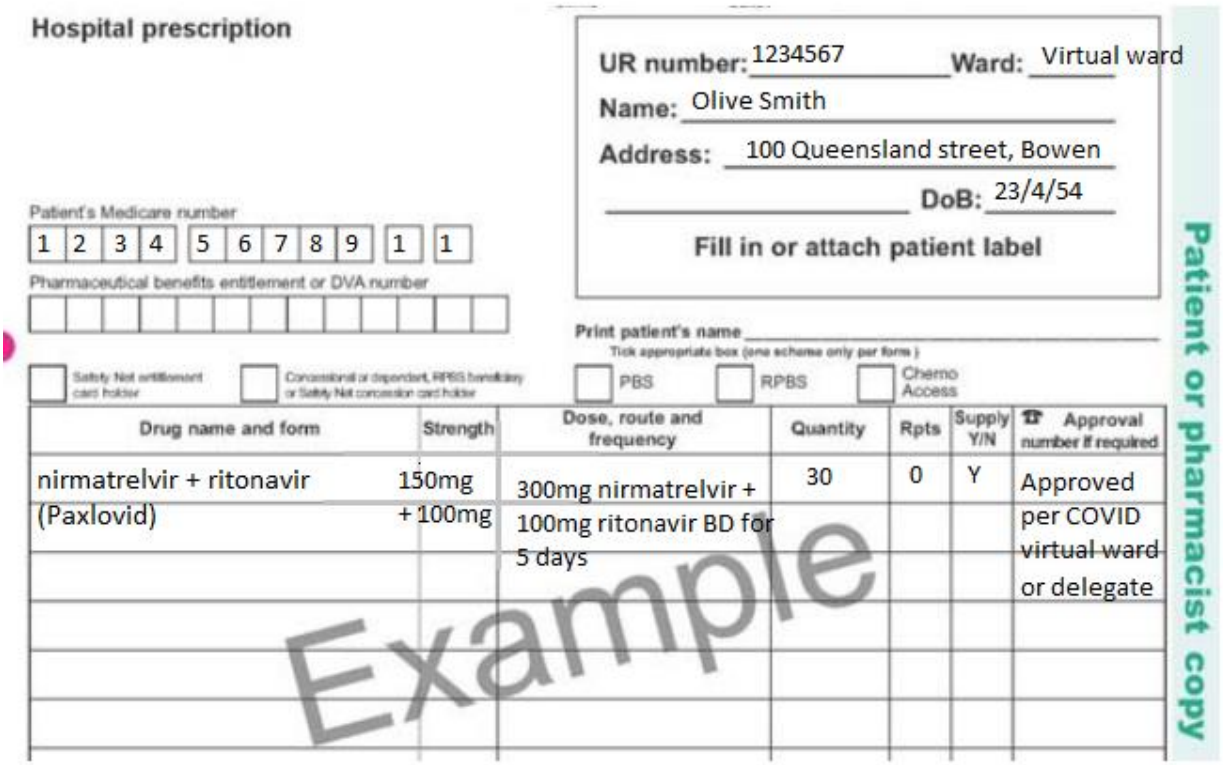
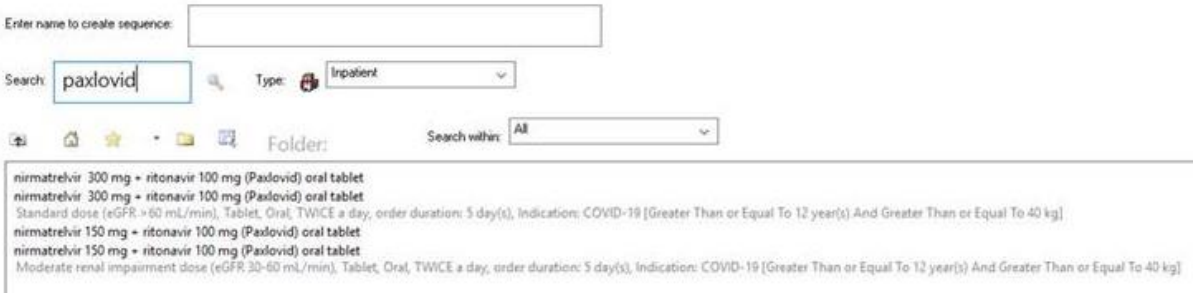


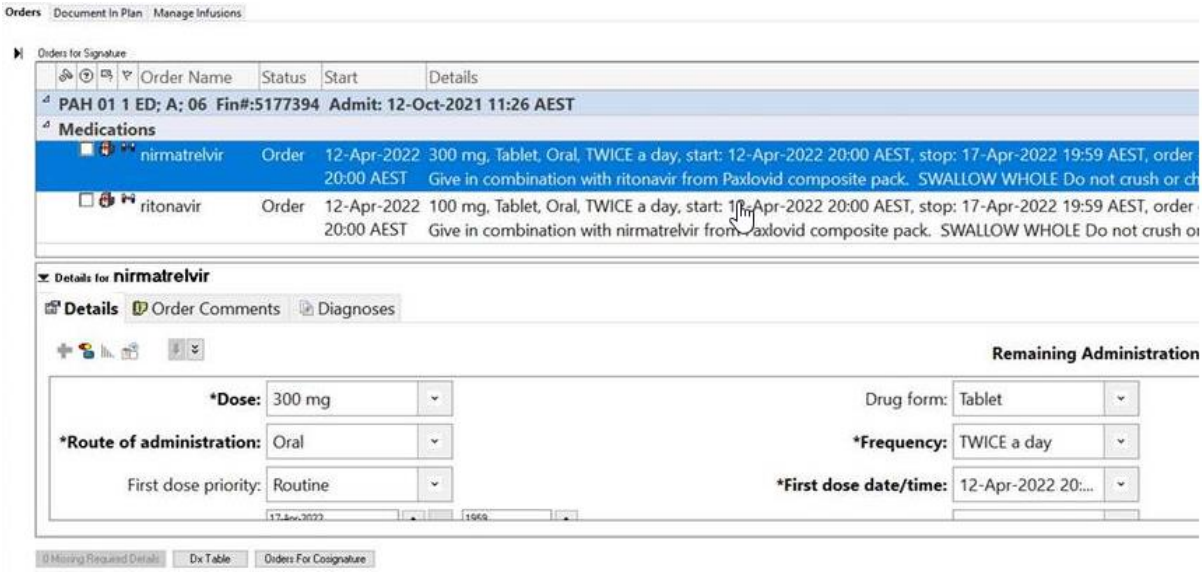
Image 3. ieMR screenshots – inpatient prescribing

Nirmatrelvir and ritonavir are ordered as a single combined therapy however, to allow each drug to be signed off as administered, they will drop into the MAR as separate orders.

- In the Orders window:



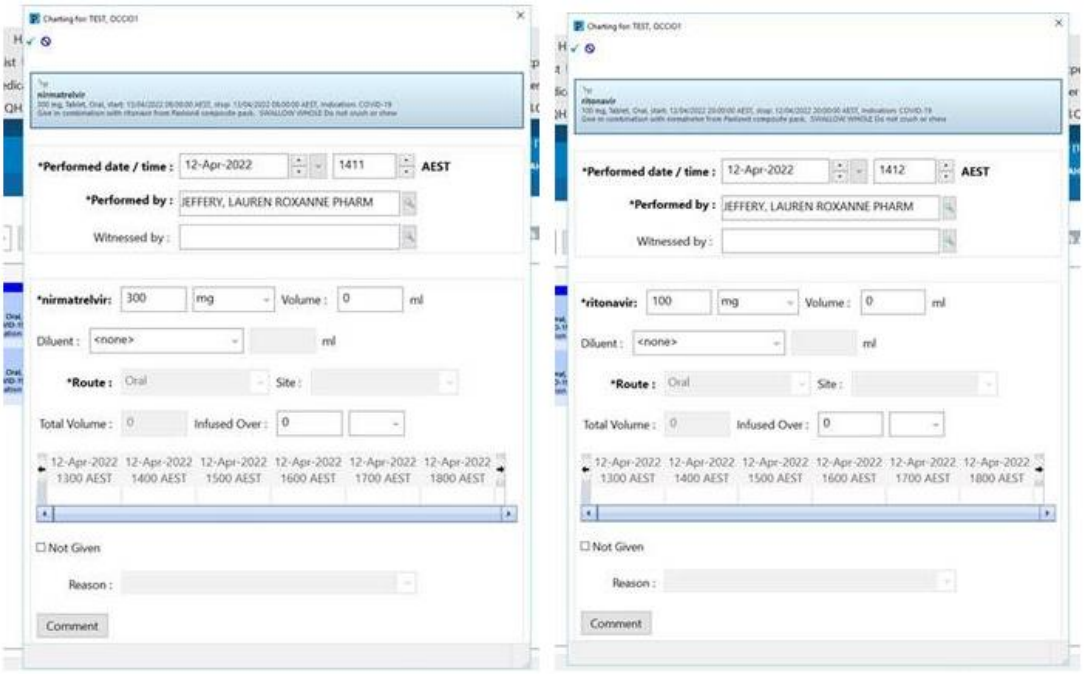
- On the scratchpad: orders appear separately



- Orders on the MAR – note that orders on the MAR are listed alphabetically and if there are other orders, they may not appear together.

Medications	15-Apr-2022 08:00 AEST	14-Apr-2022 20:00 AEST
Scheduled		
nirmatrelvir **300 mg, Tablet, Oral, TWICE a day, start: 14/04/2022 20:00:00 AEST, stop: 19/04/2022 19:59:00 AEST, order duration: 5 day(s), Indication: COVID-19** **Give in combination with ritonavir from Paxlovid composite pack. SWALLOW WHOLE Do not crush or chew**	300 mg Not given within 5 days.	**300 mg** **Not given within 5 days.**
nirmatrelvir		
ritonavir **100 mg, Tablet, Oral, TWICE a day, start: 14/04/2022 20:00:00 AEST, stop: 19/04/2022 19:59:00 AEST, order duration: 5 day(s), Indication: COVID-19** **Give in combination with nirmatrelvir from Paxlovid composite pack. SWALLOW WHOLE Do not crush or chew**	100 mg Not given within 5 days.	**100 mg** **Not given within 5 days.**
ritonavir		

- MAR administration windows

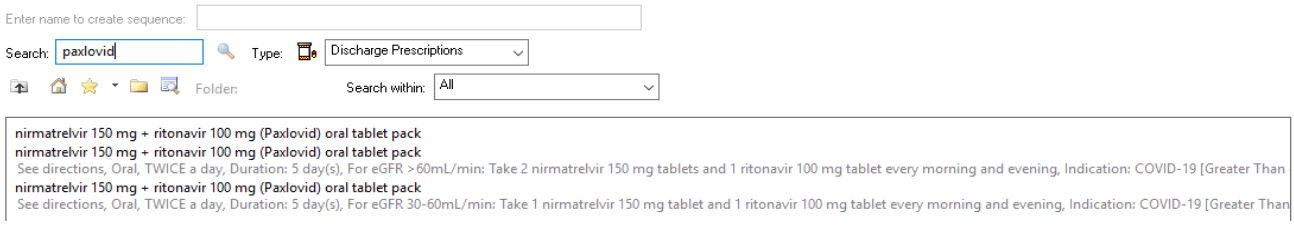


- MAW window

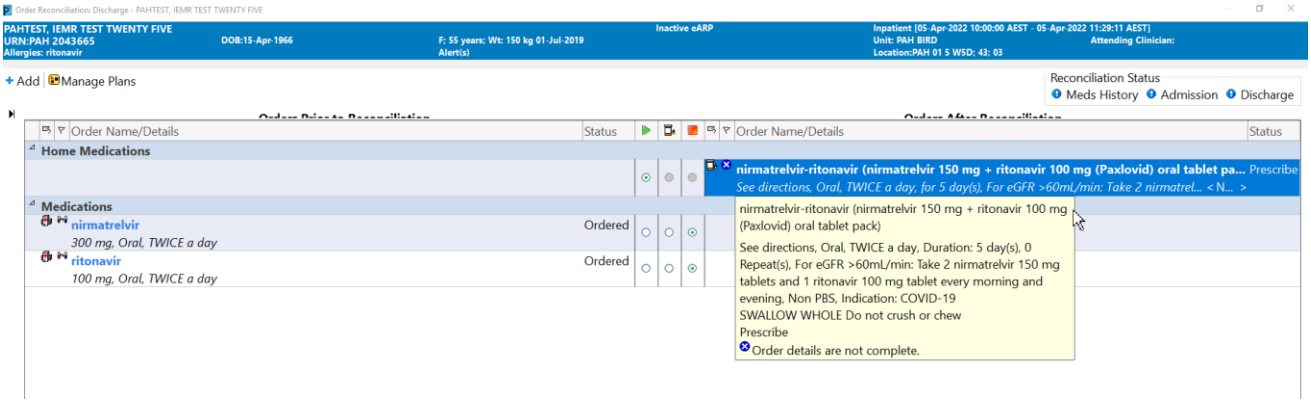
Image 4. ieMR discharge prescribing

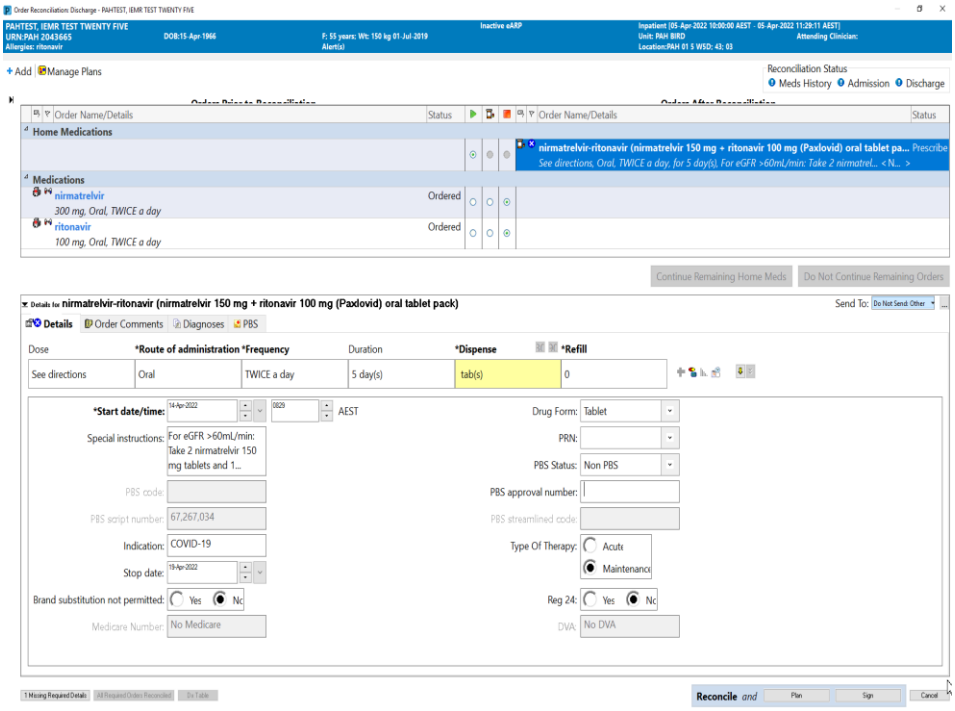
Discharge reconciliation (note that individual inpatient orders are ceased, and a composite pack is ordered on discharge)

- Orders window



- Discharge reconciliation window





10. Version control

Version	Amendments	Author/s	Approved
v 1-0	New document	Amy Legg Paul Griffin Tina Patterson	Approved: Feb 2022
v 1-1	Endorsed at COVID-19 Therapeutics Working Group	CTWG	08/02/2022
v 1-2	Approved for publication: Keith McNeil A/Deputy Director-General, CMO and CCIO Prevention Division		11/02/2022
v 1-3	S 6.1 Dose and duration: • Additional advice on modifying packaging for patients requiring dose reduction in renal impairment, crushing tablets, where to check drug interactions if not in Uni of Liverpool DDI checker and what to do if a patient misses a dose. • Changed risk factor from COPD to PD to include significant bronchiectasis • Removed non-immunosuppressive drugs based on respiratory feedback • Added Aboriginal or Torres Strait Islanders over 55 years for priority cohort • Removed the asthma biologics: benralizumab, mepolizumab, omalizumab and dupilumab and other anti-IL-17, anti-IL-23, anti-IL-6, anti-integrins, anti-TNF and checkpoint inhibitors, these agents are not anticipated to reduce the response to COVID-19 vaccination • Added prescribing examples • Added information on how to manage drug interactions	Amy Legg Tina Patterson	COVID-19 Therapeutics Working Group 5/04/2022
v 1-3	Approved for publication: Keith McNeil A/Deputy Director-General, CMO and CCIO Prevention Division		17/04/2022