

Nirmatrelvir plus Ritonavir (Paxlovid[®]) Drug Monograph

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| Nirmatrelvir plus Ritonavir (Paxlovid®) ^{1,7,15,16} ID Approval and patient consent required (verbal or written) For more detailed information on the use of nirmatrelvir plus ritonavir in patients with COVID-19 visit the product information available on the TGA website | |
|--|--|
| Drug Class | <ul style="list-style-type: none"> Nirmatrelvir is a protease inhibitor that blocks the activity of the SARS-CoV-2-3CL protease thus inhibiting viral replication. Low dose ritonavir is given concurrently with nirmatrelvir as a 'booster' to maintain nirmatrelvir plasma levels during treatment through inhibition of the CYP3A4 mediated metabolism of the nirmatrelvir. |
| Indications | <ul style="list-style-type: none"> First line treatment of mild COVID-19 for non-pregnant adults who: <ul style="list-style-type: none"> do NOT require supplemental oxygen AND are ≤ 5 days since symptom onset AND are immunosuppressed (regardless of vaccination status) OR are not vaccinated or do not have an up-to-date vaccination status with one or more risk factors for severe or critical illness Check for contraindications and drug interactions before prescribing. Treatment should not be commenced in hospitalised patients with severe or critical COVID-19 illness, however the course can be completed if commenced prior to initiation of supplemental oxygen or hospitalisation. |
| Contra-indications | <ul style="list-style-type: none"> Hypersensitivity to nirmatrelvir or ritonavir or any of the excipients listed in the product information. Children less than 18 years old Pregnancy – the use of nirmatrelvir plus ritonavir in pregnant women is not recommended as there is no human data to evaluate the drug-associated risk of adverse developmental outcomes. Women of childbearing potential should be advised to use effective contraception for the duration of treatment and for 7 days after the last dose of nirmatrelvir plus ritonavir. These recommendations are based on animal studies, the use of nirmatrelvir has not been assessed in human trials. Breastfeeding – limited data. Based on the potential for adverse reactions on the infant, breastfeeding is not recommended during AND for 7 days after treatment Contraception – Ritonavir may reduce the efficacy of combined hormonal contraceptives therefore alternative contraceptive methods or additional barrier protection is advised during treatment and for one full menstrual cycle after completing the nirmatrelvir plus ritonavir course. Severe renal impairment (eGFR < 30 mL/min) – avoid due to insufficient data. A dose reduction is required for patients with moderate renal impairment. Severe hepatic impairment – avoid due to insufficient data. Solid organ transplant recipients Drug interactions <ul style="list-style-type: none"> Co-administration of medications that are highly dependent on CYP3A4 for clearance and could be associated with serious/life-threatening reactions with elevated serum concentrations. See below for examples. Co-administration of medications which are potent CYP3A4 inducers which can result in significantly reduced plasma concentrations of nirmatrelvir + ritonavir and could be associated with loss of virologic response and possible resistance. See below for examples. |

| | |
|--|---|
| Precautions | <ul style="list-style-type: none"> Exercise caution in patients with a history of anaphylaxis to other medicines. Hepatotoxicity - Caution should be exercised in patients with pre-existing liver disease, or hepatitis. Hepatic transaminase elevations, clinical hepatitis and jaundice have been reported in patients using ritonavir. Risk of HIV-1 Resistance Development - Due to the co-administration of low dose ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.. |
| Storage and presentation | <ul style="list-style-type: none"> This is a combination therapy. The two components are provided as individual, co-packaged medications. Each package contains 30 tablets in total; 20 x 150mg nirmatrelvir tablets, and 10 x 100mg ritonavir tablets. This is the supply required to complete the standard adult 5-day course. Store at room temperature, less than 25°C |
| Dose | <ul style="list-style-type: none"> eGFR > 60mL/min/1.73m²: Nirmatrelvir 300mg (two 150mg tablets) with ritonavir 100mg (one 100mg tablet) taken together orally every 12 hours for 5 days eGFR 30-60 mL/min/1.73m²: Nirmatrelvir 150mg (one 150mg tablet) with ritonavir 100mg (one 100mg tablet) taken together orally every 12 hours for 5 days eGFR < 30 mL/min/1.73m²: Not recommended – insufficient data <p>No dose adjustment is required for patients with mild or moderate hepatic impairment. Avoid using in patients with severe hepatic impairment.</p> <ul style="list-style-type: none"> 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 |
| Administration | <ul style="list-style-type: none"> Swallow the tablets whole with or without food. Do not chew, break or crush the tablets. The daily blister for Paxlovid® contains two separated parts each containing 2 tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose. Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours. |
| Monitoring | <ul style="list-style-type: none"> Baseline creatinine, electrolytes and urea, LFTs and complete blood exam Monitor the patient for adverse effects 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 | <ul style="list-style-type: none"> It may be difficult to distinguish between adverse effects of nirmatrelvir or ritonavir and the signs and symptoms of COVID-19. As a new medication, adverse reactions to nirmatrelvir continue to be investigated. Refer to the Paxlovid® product information for a complete list of possible adverse effects. To date the most common adverse reactions reported include: <ul style="list-style-type: none"> altered sense of taste headache diarrhoea vomiting hypertension myalgia Suspected or confirmed adverse reactions should be reported via Safety Learning System and also via the Therapeutic Goods Administrations adverse effects online form: TGA adverse event reporting |
| Patient Information / consent forms | <ul style="list-style-type: none"> Nirmatrelvir pul ritonavir patient information leaflets can be found here Examples of generic patient consent forms can be found here |

Drug Interactions

- Ritonavir has many drug-drug and drug-herbal interactions which are complex and can be difficult to predict. Ritonavir is known to inhibit and induce CYP3A4 as well as many other CYP enzymes. It is also a strong inducer of UGTs (mediate glucuronidation).
- Always check the [University of Liverpool COVID-19 resource page](#) prior to prescribing nirmatrelvir plus ritonavir.
- Some of the more significant interactions are listed below however this is not an exhaustive list and information may change over time. Where it states 'consider risk vs benefit' refer to the [Australian Medicines Handbook](#), the [Liverpool resource page](#) or the Paxlovid® [product information for](#) more information on the mechanism of the interaction.

| Medicine | Recommendation | Medicine | Recommendation |
|-----------------|--------------------------|----------------|--------------------------|
| Abemaciclib | Consider risk vs benefit | Acalabrutinib | Consider risk vs benefit |
| Apalutamide | Consider risk vs benefit | Amiodarone | Do not use |
| Avanafil | Do not use | Apixaban | Do not use* |
| Bosentan | Do not use | Bedaquiline | Consider risk vs benefit |
| Carbamazepine | Do not use | Budesonide | Consider risk vs benefit |
| Ciclosporin | Do not use | Ceritinib | Consider risk vs benefit |
| Clonazepam | Do not use | Cisapride | Do not use |
| Clozapine | Do not use | Clopidogrel | Do not use* |
| Contraceptives | Consider risk vs benefit | Colchicine | Do not use |
| Delamanid | Consider risk vs benefit | Dabigatran | Consider risk vs benefit |
| Diazepam | Do not use* | Dexamphetamine | Consider risk vs benefit |
| Disopyramide | Do not use | Digoxin | Consider risk vs benefit |
| Domperidone | Do not use* | Dronedarone | Do not use |
| Encorafenib | Consider risk vs benefit | Eletriptan | Consider risk vs benefit |
| Eplerenone | Do not use | Enzalutamide | Consider risk vs benefit |
| Everolimus | Do not use | Ergometrine | Do not use |
| Flecainide | Do not use | Fentanyl | Consider risk vs benefit |
| Ibrutinib | Consider risk vs benefit | Fluticasone | Consider risk vs benefit |
| Ivabradine | Do not use | Illegal drugs | Check Liverpool page |
| Lamotrigine | Consider risk vs benefit | Ketoconazole | Consider risk vs benefit |
| Letermovir | Consider risk vs benefit | Lercanidipine | Do not use |
| Lurasidone | Do not use | Levothyroxine | Consider risk vs benefit |
| Methylphenidate | Consider risk vs benefit | Methadone | Consider risk vs benefit |
| Neratinib | Do not use | Midazolam | Do not use |
| Phenobarbital | Do not use | Pethidine | Do not use |
| Piroxicam | Do not use | Phenytoin | Do not use |
| Pimozide | Do not use | Primidone | Do not use |
| Quinidine | Do not use | Quetiapine | Do not use |
| Rifampicin | Do not use | Rifabutin | Consider risk vs benefit |
| Rivaroxaban | Do not use* | Riociguat | Consider risk vs benefit |
| Salmeterol | Do not use* | Rosuvastatin | Consider risk vs benefit |
| Simvastatin | Do not use* | Sildenafil | Do not use |
| Sodium fusidate | Do not use | Sirolimus | Do not use |
| Tacrolimus | Do not use | St John's Wort | Do not use |
| Theophylline | Consider risk vs benefit | Tadalafil | Do not use |
| Vardenafil | Do not use | Ticagrelor | Do not use |
| Venetoclax | Do not use | Valproate | Consider risk vs benefit |
| Vincristine | Consider risk vs benefit | Vinblastine | Consider risk vs benefit |
| Warfarin | Consider risk vs benefit | Voriconazole | Consider risk vs benefit |

*unless medicine can be safely stopped for 8 days. For more information re when medications can be recommenced check [University of Liverpool COVID-19 resource page](#)

2. Assessing

Assessing a patient for nirmatrelvir plus ritonavir (Paxlovid®)⁷ - contraindications and drug interaction considerations

Modified from University of Liverpool – COVID-19 Drug Interactions

Contraindications to nirmatrelvir plus ritonavir

- Age < 18 years
- Pregnant or breastfeeding
- Solid organ transplant recipients
- Severe renal impairment (eGFR < 30mL/min)
- Severe liver disease (i.e. Child Pugh Class C)
- Unable to swallow tablets
- Cognitively impaired or unable to manage medications
- Unable to store medications below 25°C
- Prescribed any of the medications **below**

| | |
|----------------|---|
| Amiodarone | Midazolam (oral) |
| Aliskiren | Neratinib |
| Apixaban* | Pethidine |
| Avanafil | Phenobarbital |
| Bosentan | Primidone |
| Carbamazepine | Pimozide |
| Ciclosporin | Phenytoin |
| Cisapride | Quetiapine |
| Clonazepam | Quinidine |
| Clopidogrel* | Rifampicin |
| Clozapine | Rivaroxaban* |
| Colchicine | Salmeterol* |
| Diazepam* | Sildenafil (for pulmonary hypertension) |
| Disopyramide | Simvastatin* |
| Domperidone* | Sirolimus |
| Dronedarone | Sodium fusidate |
| Eplerenone | St John's Wort |
| Everolimus | Tacrolimus |
| Ergometrine | Tadalafil (for pulmonary hypertension) |
| Flecainide | Ticagrelor |
| Ivabradine | Vardenafil (for pulmonary hypertension) |
| Lercanidipine* | Venetoclax |
| Lurasidone | |

*unless medicine can be safely stopped for 8 days. For more information on when medications can be recommended check [University of Liverpool COVID-19 resource page](#). Note: list of medications is not exhaustive and may change.

No

Check <http://www.covid19-druginteractions.org> and/or product information to check for potential drug interactions including:

- Over the counter medications including all herbal and vitamin supplements
- Recreational drugs
- Other medications including medications given infrequently or in a hospital setting including:
 - Chemotherapy or other biologic/targeted immune therapy in the last month
 - Opiate substitution
 - HCV/HBV/HIV treatment
 - Hormonal contraceptives (except implant/depot)
 - Steroid injections
 - Depot antipsychotics
 - Multiple sclerosis treatment

ANY RED or AMBER interactions?

Yes

Review interaction information available on University of Liverpool COVID-19 resource page and consider the following things:

- Can the medicine be safely withheld for 8 days? e.g. simvastatin
- Can a dose adjustment be easily made? (take into account patient understanding, use of compliance aids such as webster packs and whether different strengths of medication(s) will be required)
- Will the patient understand if advised of adverse reactions to monitor for and what to do if they occur?
- How long since intervention has occurred? i.e. clopidogrel

Clinical decision based on all the individual patient information, discussion with specialist if required and patient to determine if nirmatrelvir plus ritonavir is appropriate.

Medications unlikely to interact or to have a significant interaction with nirmatrelvir plus ritonavir (Paxlovid®)

ACE inhibitors
 Acid reducing agents (antacids, PPIs, histamine receptor antagonists)
 Aspirin
 Azathioprine
 Beta blockers
 Corticosteroids (oral, inhaled, topical)
 Fluvastatin
 Furosemide
 Gabapentin
 HRT/Contraceptive implant or depot
 Immunoglobulin
 Inhalers (except salmeterol)
 Insulin
 Levothyroxine
 Metformin
 Methotrexate
 Monoclonal antibodies (mAbs)
 Mycophenolate
 Non-steroidal anti-inflammatories (NSAIDs)
 Pravastatin
 Pregabalin

Yes, nirmatrelvir plus ritonavir (Paxlovid®)

Nirmatrelvir plus ritonavir (Paxlovid®) dosing

For eGFR > 60 mL/min:
 300mg nirmatrelvir (2x150mg capsules) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days
For eGFR ≥ 30 to < 60mL/min:
 150mg nirmatrelvir (1x150mg capsule) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days
eGFR < 30: not recommended

No nirmatrelvir plus ritonavir (Paxlovid)

No nirmatrelvir plus ritonavir (Paxlovid®)

3. Definitions/Acronyms/Abbreviations

| | |
|------|---------------------------------------|
| BMI | Body Mass Index |
| COPD | Chronic obstructive pulmonary disease |
| eGFR | estimated Glomerular Filtration Rate |
| GI | Gastrointestinal |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | Human Immunodeficiency Virus |
| ID | Infectious Diseases |
| IV | Intravenous |
| LFTs | Liver function tests |
| NMS | National Medical Stockpile |
| NYHA | New York Heart Association |

4. Resources

- [National COVID-19 Clinical Evidence Taskforce \(The Australian Living Guidelines\)](#)
- [COVID-19 Resources: NSW Therapeutic Advisory Group](#)
- [COVID-19 \(SARS-COV-2\) – Management Guide \(CALHN-PRC05409\)](#)
- [Anaphylaxis: Management Guidelines \(CALHN-OWI04038\)](#)
- [COVID-19: Disease-modifying therapy recommendations for hospitalised adults \(CALHN-GDE05778\)](#)
- [CALHN COVID-19 internet page](#)
- [World Health Organisation. Therapeutics and COVID-19: Living Guideline](#)
- [Australian Technical Advisory Group on Immunisation \(ATAGI\)](#)
- [Clinical Excellence Commission: Medication Safety Updates](#)
- [COVID-19 Treatment: Nirmatrelvir-Ritonavir \(Paxlovid®\) \(IH-CIS05842\)](#)
- [COVID-19 Resources: Medicines Use in the treatment of COVID-19 – Consent Forms](#)

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6 Document History

| Version | Date approved | Approved by | Amendment notes |
|---------|---------------|--|--|
| 3.0 | 12/04/22 | CALHN Drug and Therapeutics Committee South Australian Medicines Advisory Committee | Monograph updated to align with updated COVID-19: Medication management of Mild Illness in the Outpatient Setting v3.0 |
| 2.0 | 18/02/22 | CALHN Drug and Therapeutics Committee COVID-19 Medicines Advisory Group | Add molnupiravir and nirmatrelvir plus ritonavir. Added link on sotrovimab monograph for breastfeeding advice. |
| 1.0 | 19/01/22 | South Australian Medicines Advisory Committee | New guideline to provide a pathway for the medication management of mild COVID-19 illness in the outpatient setting. |