Fact Sheet

Nirmatrelvir plus ritonavir (Paxlovid®)

Information for prescribers and pharmacists

Nirmatrelvir plus ritonavir (Paxlovid®) was provisionally registered by the Therapeutic Goods Administration in January 2022 for the treatment of adults with mild COVID-19. Currently it is available at public hospital pharmacy departments via the National Medical Stockpile (NMS). If you think a patient may be eligible for treatment then you can refer them here.

How nirmatrelvir plus ritonavir works

Nirmatrelvir is an antiviral medication 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.

Ritonavir is not active against SARS CoV-2 but is a “boosting agent” and potent CYP3A4 inhibitor which slows nirmatrelvir metabolism thereby increasing its concentration.

What is the evidence for nirmatrelvir plus ritonavir?

Nirmatrelvir plus ritonavir is a highly effective outpatient therapy based on available data but there is high risk of harm if drug interactions are not mitigated.

Based on evidence from the EPIC-HR study nirmatrelvir plus ritonavir was found to reduce hospitalisations in high-risk adult patients with laboratory proven COVID-19 infection, who were not on supplemental oxygen, and who were treated within 5 days of symptom onset. The EPIC-HR trial demonstrated 85% relative risk reduction of disease progression leading to hospitalisation or death at 28 days compared with placebo.

Who should be prescribed nirmatrelvir plus ritonavir?

Decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the patient’s individual risk of severe disease, age and risk factors, COVID-19 vaccination status and time since vaccination.

Currently nirmatrelvir plus ritonavir is NOT recommended during pregnancy, in women of childbearing potential not using contraception or in paediatric patients under 18 years of age.

Eligibility Criteria

As per the National COVID-19 Clinical Evidence Taskforce Guidelines and SA Health Guidelines, adult patients are eligible for treatment with nirmatrelvir plus ritonavir if:

- Confirmed as being COVID-19 positive by either a PCR test or have a positive Rapid Antigen Test PLUS symptoms of mild COVID-19 illness **AND**
- Have been symptomatic for ≤ 5 days **AND**
- Don’t have an oxygen requirement **AND**
- Unvaccinated or vaccine status not up to date against COVID-19 (currently one dose or >3 months from 2nd dose) **AND** have risk factor(s) for developing severe disease **OR**
  Immunosuppressed (regardless of vaccination status) with limited access to a COVID Care Centre for monoclonal antibody infusion or patient preference for treatment with an oral antiviral medication
  AND

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SA Health

- Have no contraindications to the use of nirmatrelvir plus ritonavir.

Contraindications

- Hypersensitivity to nirmatrelvir plus ritonavir or to any of the excipients
- Drug interactions (see below)
- Age < 18 years
- Severe renal impairment (eGFR < 30mL/min)
- Severe liver disease (i.e. Child Pugh Class C)
- Unable to swallow tablets whole
- Unable to store medications below 25°C

Special Warnings and Precautions for Use

Use in pregnancy (Category B3):

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

Women of childbearing potential should use effective contraception and avoid becoming pregnant for the duration of treatment and for seven days after stopping the medication.

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 course and until one menstrual cycle after stopping nirmatrelvir with ritonavir.

Use in breastfeeding

It is not known how much nirmatrelvir passes into breast milk.

Low levels of ritonavir are found in breast milk and the serum of breastfed infants. No adverse reactions to ritonavir have been reported in breastfed infants.

Currently, the manufacturer advises that breastfeeding is not recommended during treatment with nirmatrelvir/ritonavir and for 7 days after the last dose due to the potential for adverse reactions on the infant.

An individual risk assessment should be conducted for each patient, considering the benefits of any treatment and the benefits of continued breastfeeding.

Paediatric patients

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.

HIV

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

Drug Interactions:

A thorough review of drug-drug interactions is required prior to prescribing nirmatrelvir and ritonavir as ritonavir is a potent inhibitor of CYP3A4 isoenzyme and various drug transporters (e.g., P-glycoprotein). Ritonavir and nirmatrelvir are both CYP3A4 substrates.

Nirmatrelvir plus ritonavir is contraindicated in patients taking drugs that are: Highly metabolized by CYP3A4 where elevated concentrations can be life-threatening. Potent CYP3A4 inducers which may reduce the effectiveness of nirmatrelvir plus ritonavir and

contribute to the development of drug resistance. For more information please review The University of Liverpool COVID-19 interaction checker or SA Health guidelines.

Nirmatrelvir plus ritonavir dosing

For normal renal function (eGFR≥ 60mL/min): Nirmatrelvir 300 mg (2 x 150 mg tablets) and ritonavir 100 mg (1 x 100 mg tablet) taken orally every 12 hours for five days.

For moderately impaired renal function (eGFR 30mL/min to 60mL/min): Nirmatrelvir 150 mg (1 x 150 mg tablets) and ritonavir 100 mg (1 x 100 mg tablet) taken orally every 12 hours for five days

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

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

Severe renal impairment:

Nirmatrelvir plus ritonavir is contraindicated in patients with eGFR < 30ml/min.

Hepatic impairment:

No dosage adjustment is required for patients with hepatic impairment.

What if a patient misses a dose:

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.

Adverse Effects

Common side effects of nirmatrelvir plus ritonavir are generally mild and can include taste disturbance, diarrhoea, hypertension, myalgia, vomiting and headache. Not many people have taken this drug, and it is still being studied -so it is possible that all the side effects are not yet known, or that rare, but serious side effects may occur. It can also cause an elevation in d-dimer.

As nirmatrelvir plus ritonavir is 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. Nirmatrelvir plus ritonavir is subject to additional monitoring in Australia to allow quick identification of new safety information. Healthcare professionals should report any suspected adverse events to the TGA at http://www.tga.gov.au/reporting-problems

Presentation and storage

Paxlovid® consists of 2 medicines packaged together:

- Nirmatrelvir (pink) 150 mg tablet PLUS Ritonavir (white) 100 mg tablet
- Each carton contains 5 blister cards. One blister card is used each day. The full course of treatment is 5 days.

Further information

Clinical resources

National COVID-19: Clinical Evidence Taskforce

NPS Medicine Wise: COVID-19: Information to support healthcare professionals and consumers

SA Health: COVID-19 Mild illness: Treatments and Referrals

Clinical Excellence Commission Medication Safety Updates

ATAGI

University of Liverpool COVID-19 interaction checker

Patient information

Clinical Excellence Commission: Information for patients and carers

For more information

Medicines Information Service
T: (08) 8161 7555
Monday to Friday, 9:00am to 5:00pm
E: medinfo@sa.gov.au
www.sahealth.sa.gov.au

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