SA Health

# COVID-19: Medication management of Mild Illness in the Outpatient Setting

Statewide Clinical Guideline - Adoption of CALHN Guideline

Endorsed by CALHN Drugs and Therapeutics Committee: 29/04/2024

Version 5.1

Approval date: 29/04/2024

Government of South Australia | Health
Central Adelaide Local Health Network

# GUIDELINE

| | | | | |
|---|---|---|---|---|
| **Reference** | CALHN-GDE05808 | | | |
| **Title** | COVID-19: Medication Management of Mild Illness in the Outpatient Setting | | | |
| **Scope** | CALHN staff managing COVID-19 mild illness in the outpatient setting | | | |
| **Document owner** | Infectious Diseases – Speciality Medicine 2 | | | |
| **Lead contact** | Caitlin Wallace, Antimicrobial Stewardship Pharmacist, CALHN, Health.CALHNAntimicrobialStewardship@sa.gov.au | | | |
| **Oversight committee** | CALHN Drug and Therapeutics Committee | | | |
| **Committee endorsement** | 29 April 2024 | | | |
| **Sponsor** | Dr Renjy Nelson – Head of Unit, Infectious Diseases/IPCU, CALHN | | | |
| **Sponsor approval** | 22 April 2024 | | | |
| **Priority Care Committee (PCC)** | PCC: National Standard 4 Medication Safety | | | |
| **Risk rating** | ☐ Extreme | ☐ High | ☒ Medium | ☐ Low |
| **Title and reference of parent SA Health Policy** | N/A | | | |
| **Summary** (three sentences maximum) | This guideline provides a pathway for the medication management of mild COVID-19 illness in the outpatient setting. | | | |
| **Keywords** (five to eight) | COVID-19, molnupiravir, nirmatrelvir, ritonavir, remdesivir, mild, outpatient. | | | |

| Clinical Governance | Partnering with Consumers | Preventing and Controlling Healthcare Associated Infections | Medication Safety | Comprehensive Care | Communicating for Safety | Blood Management | Recognising and Responding to Acute Deterioration |
|---|---|---|---|---|---|---|---|
| ☒ | ☐ | ☒ | ☒ | ☐ | ☐ | ☐ | ☐ |

| Version | Change summary | Next scheduled review |
|---|---|---|
| 5.1 | Non-scheduled minor review. Clarification of PBS eligibility for nirmatrelvir/ritonavir and molnupiravir for patients aged 50-69. Change in recommendations for remdesivir and nirmatrelvir/ritonavir in renal impairment. Remove classification of immunocompromised patients and insert link to PBS instead. Remove sotrovimab drug monograph. | April 2027 |
| 5.0 | Non-scheduled minor review. Patients aged > 50 years with 1 risk factor eligible for PBS treatment with nirmatrelvir/ritonavir. Removed “not up to date vaccination status” as requirement for treatment eligibility for patients < 50 years. | July 2026 |
| 4.9 | Non-scheduled review. Indications for anti-viral treatment updated to include individuals previously hospitalised with COVID-19 infection, independent of age and other risk factors. | May 2026 |
| 4.8 | Non-scheduled review. Updated eligibility for access to oral antiviral medications to be in line with PBS changes made at the start of April 2023. | April 2026 |
| 4.7 | Non-scheduled review. Updated risk factors for severe illness to be in line with changes made to the PBS in Jan 2023. Timeframe for checking blood results updated for haemodialysis patients on remdesivir. | February 2026 |
| 4.6 | Non-scheduled review. Statement added regarding use of molnupiravir and place in therapy following National Clinical Taskforce update. Flow charts on pages 7-10 updated to reflect current evidence and recommendations re molnupiravir. Updated information regarding administration of nirmatrelvir plus ritonavir in patients with swallowing difficulties. | December 2025 |

# GUIDELINE

# COVID-19: Medication Management of Mild Illness in the Outpatient Setting

## Contents Page

Introduction

Risk Factors for progressing to severe disease

Classification of immunosuppression

Treatment recommendations

- One page summary flow chart
- Immunosuppressed patients
- Patients aged ≥ 50 years or ≥ 30 years if Aboriginal and/or Torres Strait Islander
- Patients aged < 50 years or < 30 years if Aboriginal and/or Torres Strait Islander
- Pregnant patients
- Assessing patients for nirmatrelvir plus ritonavir treatment

Medication monographs

- Nirmatrelvir plus ritonavir (Paxlovid®)
- Remdesivir
- Molnupiravir

References

Appendices

- Definition of disease severity

Government of South Australia | Health Central Adelaide Local Health Network

| Title | COVID-19: Medication Management of Mild Illness in the Outpatient Setting | | | | |
|---|---|---|---|---|---|
| Reference | CALHN-GDE05808 | Version | 5.1 | Approved | 22 April 2024 |

# GUIDELINE

# COVID-19: Medication Management of Mild Illness in the Outpatient Setting

## Introduction

- Since the emergence of COVID-19 there have been significant developments in the antiviral and immunomodulatory medications recommended for patients with COVID-19.
- This guideline only addresses the use of disease-modifying treatments for COVID-19 in adult patients with mild illness who **DO NOT** require supplemental oxygen or hospitalisation for COVID-19. It is intended to guide treatment of patients in the outpatient setting including in the COVID-19 Hospital Avoidance and Supported Discharge Service (HASDS) clinic.
- This guideline **DOES NOT:**
    - provide guidance of the overall care for patients with COVID-19.
    - provide advice regarding supportive therapies recommended for COVID-19.
    - provide advice regarding disease-modifying therapies recommended for patients hospitalised with COVID-19.
    - provide information regarding the prevention of COVID-19 nor does it provide information regarding post exposure prophylaxis for COVID-19.
- For information related to the management and care of patients with COVID-19 refer to:
    - COVID-19: Disease-modifying treatment recommendations for hospitalised adult patients (CALHN-GDE05778)
    - COVID–19 (SARS–COV–2) – Management Guide (CALHN–PRC05409)
    - CALHN COVID–19 internet page
- Medication recommendations for COVID-19 can change rapidly due to medication shortages, ongoing research and as novel agents are discovered. For the most up to date Australian guidelines and recommendations refer to:
    - National COVID-19 Clinical Evidence Taskforce (The Australian Living Guidelines)
    - Clinical Excellence Commission: Medication Safety Updates
    - Pharmaceutical Benefits Scheme

## Definition of COVID-19 mild illness[1]

Adults not presenting any clinical features suggestive of moderate or severe illness or a complicated course of illness. Characteristics of mild illness include:

- No symptoms; or
- Mild upper respiratory tract symptoms; or
- Cough, new myalgia or lethargy/weakness without new shortness of breath or a reduction in oxygen saturation

See Appendix 1 for complete description of COVID-19 disease severity definition.

## Risk factors for progressing to severe or critical illness

- Immunosuppression
- Renal impairment (eGFR < 60mL/min or equivalent renal impairment for pregnant women)
- Age ≥ 50 years, or age ≥ 30 years if Aboriginal and/or Torres Strait Islander*
- Diabetes (requiring medication) or gestational diabetes (requiring medication) in pregnant women
- Obesity (BMI > 30 kg/m$^2$ or > 40 kg/m$^2$ for pregnant patients)
- Chronic liver disease (cirrhosis)
- Respiratory compromise including:
    - history of chronic bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD) or moderate-to-severe asthma requiring an inhaled steroid to control symptoms or caused by neurological or musculoskeletal disease
- Neurological conditions including stroke, dementia and demyelinating conditions
- Cardiovascular disease including coronary artery disease
- Heart failure or cardiomyopathies
- Residing in residential aged care
- Disability with multiple comorbidities and/or frailty
- Past COVID-19 infection episode resulting in hospitalisation
- 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
- Pregnancy (see page 9)

**Please note the following conditions previously listed risk factors are now included in conditions considered immunosuppressive as per the PBS**

- People with disability with multiple comorbidities and/or frailty
- Down Syndrome
- Cerebral palsy
- Congenital heart disease
- Thalassemia
- Sickle cell disease
- Other haemoglobinopathies not already listed

* Age ≥ 50 years or ≥ 30 years if Aboriginal and/or Torres Strait Islander as a risk factor for developing severe COVID-19 illness has been taken into account in the flow charts on pages 7-10 and hence is not included in the box containing risk factors for developing severe disease on those pages.

## Classification of Immunocompromised Patients

Immunocompromised patients are not expected to mount an adequate immune response to COVID-19 vaccination, or the COVID-19 infection due to their underlying conditions regardless of their vaccine status. Early access to treatment with COVID-19 antiviral medications is important for immunocompromised patients to reduce the likelihood of progression to more severe COVID-19 illness.

For more information regarding eligibility for treatment of early COVID-19 with antiviral medications for patients with immunocompromising medical conditions or taking immunosuppressive medications, see the PBS criteria here.

Government of South Australia
Health
Central Adelaide Local Health Network

| Title | COVID-19: Medication Management of Mild Illness in the Outpatient Setting |
|---|---|

# COVID-19 treatment recommendations for mild illness in non pregnant adults (see page 9 for recommendations in pregnancy)

## Eligible for oral antiviral medications via the PBS#
**Irrespective of vaccination status**

- **Immune suppressed patients**
- **Previous COVID-19 infection resulting in hospitalisation**
  (see page 6)

- **Aged ≥ 70 years irrespective of risk factors OR**
- **Aged ≥ 50 to 69 years with ≥ 2 risk factors@**
  (see page 7)

**Aboriginal or Torres Strait Islander Aged ≥ 30 years AND ≥ 1 risk factor**
**(see page 8)**

**Symptom onset ≤ 7 days**

**First line:**
**Symptom onset ≤ 5 days**
**Nirmatrelvir plus ritonavir** via PBS

**Second line:***
**Symptom onset ≤ 7 days: Remdesivir**
Via Referral to HASDS or SA Health Referral Page

**Third lineβ:**
**Symptom onset ≤ 5 days: Molnupiravir** via PBS

## Not eligible for medications via PBS¥

¥Patients with disability with multiple/significant comorbidities and/or frailty are eligible per PBS irrespective of age or vaccination status (use immunosuppressed green pathway) otherwise prescribe as below

**Aged < 50 years or < 30 years if Aboriginal or Torres Strait Islander**
**(see page 8)**

**2 risk factors**

**First line:**
**Symptom onset ≤ 5 days**
**Nirmatrelvir plus ritonavir** Non PBS^

See below if first and/or second line treatment options contraindicatedβ*

**≥ 3 risk factors**

**First line:**
**Symptom onset ≤ 5 days**
**Nirmatrelvir plus ritonavir** Non PBS^

**Second line:**
**Symptom onset ≤ 7 days Remdesivir**
Via Referral to HASDS or SA Health Referral Page

**Molnupiravir:** The National Clinical Evidence Taskforce recently recommended against routine use of molnupiravir except in specific circumstances and where all other treatment options are contraindicated OR inappropriate, based on the results of the PANORAMIC Trial. The median age of patients in the PANORAMIC trial was 56 years (younger than target treatment groups in Australia) and a reduction in time to recovery was shown for all patients and trend to reduced hospitalisation/death in patients aged ≥ 80 years. The AMS Committee note recent Victorian data which showed a reduction in hospitalisation and death in patients aged ≥ 70 years who received molnupiravir. Molnupiravir should continue to be considered when nirmatrelvir/ritonavir and/or remdesivir are contraindicated, inappropriate or inaccessible.

Supportive care alone recommended for patients who had symptom onset > 7 days earlier and those considered at low risk of progressing to severe COVID-19 illness (i.e. immunocompetent and fully vaccinated patients aged < 50 years OR patients aged ≥ 50-70 years with no risk factors for progressing to severe disease).

* For patients who have a contraindication to nirmatrelvir plus ritonavir, consider second line treatment based on likely risk of progressing to severe illness i.e. age, vaccination status, frailty, extent of comorbidity, and whether their condition is deteriorating. Molnupiravir can continue to be considered when nirmatrelvir/ritonavir and/or remdesivir are contraindicated, inappropriate or inaccessible as availability of remdesivir infusions is limited.

β Consider risk versus benefits of molnupiravir as limited evidence in patients < 70 years. For patients aged < 70 years who are contraindicated from taking nirmatrelvir plus ritonavir and/or remdesivir, only prescribe molnupiravir if benefits outweigh risks AND appropriate reproductive counselling can be provided.

**#** For patients without Medicare follow the same medication recommendations but prescribe as non-PBS^.

**^** Non-PBS Oral Antiviral Medications: When prescribed in a public hospital should be dispensed from the public hospital pharmacy due to the high cost to the patient if obtained in the community.

# COVID-19 treatment recommendations for mild illness in adults – Immunocompromised patients OR patients with previous COVID-19 infection requiring hospitalisation

**Immunocompromised patients OR patients who have previously experienced a COVID-19 infection resulting in hospitalisation irrespective of vaccination status and number of risk factors (excluding pregnancy – see page 9)**

**First Line** →

If **NO** contraindication (see page 11)
**and ≤ 5 days since symptom onset**

**Nirmatrelvir plus Ritonavir (via PBS)**

**Second Line** →

Immunosuppressed patients and **≤ 7 days since symptom onset**

**Remdesivir**
(Referral to HASDS or via SA Health referral webpage)

**Only if nirmatrelvir/ritonavir AND remdesivir both contraindicated or unavailable**

**Third Line** →

**≤ 5 days since symptom onset**
**Molnupiravir (via PBS)**

For more information regarding eligibility for treatment of early COVID-19 with antiviral medications for patients with immunocompromising medical conditions or taking immunosuppressive medications, see here.

**Dosing recommendations**
**Nirmatrelvir plus ritonavir**: **eGFR > 60 mL/min:** 300mg nirmatrelvir (2x150mg capsules) + 100mg ritonavir (1x100mg capsule) orally twice daily for 5 days.
**eGFR < 60mL/min**: 150mg nirmatrelvir (1x150mg capsule) + 100mg ritonavir (1x100mg capsule) orally twice daily for 5 days – use with caution in patients with eGFR < 30 mL/min (see drug monograph)
**Molnupiravir**: 800mg (4 x 200mg capsules) orally 12-hourly for 5 days. **Ensure appropriate reproductive counselling provided.**
**Remdesivir:** 200mg IV infusion loading dose day 1 then 100mg IV daily on day 2 and 3. Total 3 day course.

# COVID-19 treatment recommendations for mild illness in adults – Patients aged ≥ 50 years OR ≥ 30 years for Aboriginal and or Torres Strait Islander patients (excluding pregnancy – see page 9)

**All patients aged ≥ 50 years or ≥ 30 years if Aboriginal or Torres Strait Islander**

Patients with disability with multiple/significant comorbidities and/or frailty are eligible per PBS irrespective of age or vaccination status (use immunosuppressed pathway - page 6) otherwise prescribe as below.

**Irrespective of vaccination status**

**Aged ≥ 70 years (regardless of risk factors)**

**OR**

**Aged ≥ 50 to 69 years PLUS ≥ 2 risk factors (Box 1)**

**OR**

**Aged ≥ 30 years AND Aboriginal or Torres Strait Islander PLUS ≥ 1 risk factor (Box 1)**

**First Line:**

Symptom onset **≤ 5 days AND NO** contraindications

**Nirmatrelvir plus ritonavir** (via PBS)

**Second Line:**

For patients who have a contraindication to nirmatrelvir plus ritonavir consider second line treatment based on likely risk of progressing to severe illness*

**High Risk:** Symptom onset **≤ 7 days AND** contraindications to nirmatrelvir plus ritonavir

**Remdesivir**

(via Referral to HASDS or via SA Health referral webpage)

**Low Risk:** Symptom onset **≤ 5 days AND** nirmatrelvir plus ritonavir and remdesivir contraindicated or unavailable

**Molnupiravir** (via PBS)

**NOTE:** Supportive care alone may be sufficient for patients who are at **low risk of progressing to severe illness** (i.e. patients aged ≥ 50 years but < 70 years with no risk factors for progressing to severe illness (Box 1), or for those patients experiencing mild symptoms for > 7 days).

**^Non PBS Oral Antiviral Medications:** When prescribed in a public hospital should be dispensed from the public hospital pharmacy due to the high cost to the patient if obtained in the community.

**Box 2: Dosing recommendations**

**Nirmatrelvir plus ritonavir**:

**eGFR > 60 mL/min:** 300mg nirmatrelvir (2x150mg capsules) + 100mg ritonavir (1x100mg capsule) orally twice daily for 5 days.

**eGFR < 60mL/min**: 150mg nirmatrelvir (1x150mg capsule) + 100mg ritonavir (1x100mg capsule) orally twice daily for 5 days. Use with caution in patients with eGFR < 30 mL/min (see drug monograph)

**Molnupiravir**: 800mg (4 x 200mg capsules) orally 12-hourly for 5 days. **Ensure appropriate reproductive counselling provided.**

**Remdesivir:** 200mg IV infusion loading dose day 1 then 100mg IV daily on day 2 and 3. Total 3 day course. **If eGFR < 30mL/min and/or on dialysis** discuss with Clinical Pharmacy, Infectious Diseases or Renal (see drug monograph for more detail).

**Box 1: Risk factors for progressing to severe illness**

- Renal impairment (eGFR < 60mL/min)
- Diabetes (requiring medication)
- Obesity (BMI > 30 kg/m$^2$)
- Chronic liver disease (cirrhosis)
- Coronary artery disease
- Heart failure and cardiomyopathies
- Respiratory compromise including history of chronic bronchitis, cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, moderate-to-severe asthma requiring an inhaled steroid to control symptoms or caused by neurological or musculoskeletal disease
- Neurological conditions e.g. stroke, dementia, demyelinating conditions (including multiple sclerosis)
- Residential aged care
- Disability with multiple comorbidities and/or frailty
- Past COVID-19 infection episode resulting in hospitalisation
- 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

The following "High risk conditions" are now included in the list of immunocompromised conditions as per PBS criteria:

- People with disability with multiple comorbidities and/or frailty
- Down Syndrome
- Cerebral palsy
- Congenital heart disease
- Thalassemia
- Sickle cell disease
- Other haemoglobinopathies not already listed

*Consider risk and appropriate second line treatment based on age, vaccination status, frailty, extent of comorbidities and whether patient condition is deteriorating .

Government of South Australia | Health Central Adelaide Local Health Network

| Title | COVID-19: Medication Management of Mild Illness in the Outpatient Setting | | | | |
|---|---|---|---|---|---|
| Reference | CALHN-GDE05808 | Version | 5.1 | Approved | 22 April 2024 |

# COVID-19 treatment recommendations for mild illness in adults – Patients aged < 50 years OR < 30 years for Aboriginal and/or Torres Strait Islander patients with risk factors (excluding pregnancy – see page 9)

**Aged < 50 years or < 30 years if Aboriginal and/or Torres Strait Islander**

**2 risk factors** for progressing to severe illness (Box 1)

**First Line:**
If symptom onset **≤ 5 days AND NO** contraindications

**Nirmatrelvir plus ritonavir**
(Non PBS^)

See Box 2 for patients contraindicated from taking nirmatrelvir plus ritonavir

**≥ 3 risk factors** for progressing to severe illness (Box 1)

**First line:**
Symptom onset **≤ 5 days AND NO** contraindications

**Nirmatrelvir plus ritonavir**
(Non PBS^)

**Second Line:** Symptom onset **≤ 7 days**
**Remdesivir:**
(via SA Health referral webpage)

See Box 2 for patients contraindicated from taking nirmatrelvir plus ritonavir AND remdesivir

**Box 2:** Consider risk versus benefits of molnupiravir as limited evidence in patients <70 years. For patients who are contraindicated from taking nirmatrelvir/ritonavir and/or remdesivir only prescribe molnupiravir if benefits outweigh risks AND appropriate reproductive counselling can be provided.

**NOTE:** Supportive care alone is likely sufficient for patients who are at **low risk of progressing to severe illness** (i.e. patients aged ≥ 50 years but < 70 years with no risk factors for progressing to severe illness (Box 1), or for those patients experiencing mild symptoms for > 7 days).

**Box 3: Dosing recommendations**
**Nirmatrelvir plus ritonavir**: **eGFR > 60 mL/min:** 300mg nirmatrelvir (2x150mg capsules) + 100mg ritonavir (1x100mg capsule) orally twice daily for 5 days. **eGFR < 60mL/min**: 150mg nirmatrelvir (1x150mg capsule) + 100mg ritonavir (1x100mg capsule) orally twice daily for 5 days. Use with caution in patients with eGFR < 30 mL/min (see drug monograph on page 13)
**Molnupiravir**: 800mg (4 x 200mg capsules) orally 12-hourly for 5 days
**Remdesivir:** 200mg IV infusion loading dose day 1 then 100mg IV daily on day 2 and 3.

**Box 1: Risk factors for progressing to severe illness**
- Renal impairment (eGFR < 60mL/min)
- Diabetes (requiring medication)
- Obesity (BMI > 30 kg/m$^2$)
- Chronic liver disease (cirrhosis)
- Coronary artery disease
- Heart failure and cardiomyopathies
- Respiratory compromise including history of chronic bronchitis, cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, moderate-to-severe asthma requiring an inhaled steroid to control symptoms or caused by neurological or musculoskeletal disease
- Neurological conditions e.g. stroke, dementia, demyelinating conditions (including multiple sclerosis)
- Residential aged care
- Disability with multiple comorbidities and/or frailty
- Past COVID-19 infection episode resulting in hospitalisation
- 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

Please note the following "High risk conditions" are now included in the list of immunocompromised conditions as per PBS criteria
- People with disability with multiple comorbidities and/or frailty
- Down Syndrome
- Cerebral palsy
- Congenital heart disease
- Thalassemia
- Sickle cell disease
- Other haemoglobinopathies not already listed

**^Non PBS Oral Antiviral Medications:** When prescribed in a public hospital should be dispensed from the public hospital pharmacy due to the high cost to the patient if obtained in the community.

# COVID-19 treatment recommendations for mild illness in adults – Pregnancy

## Pregnant Patients

Immunosuppressed regardless of vaccination status **OR**
Not up to date vaccination status (Box 2) with risk factor/s for progressing to severe illness (Box 1)
**All patients must be ≤ 7 days since symptom onset**

**First Trimester:** Contact Infectious Diseases
**Second and Third Trimester:**
**Remdesivir**
(via referral to HASDS or SA Health referral webpage)
**PLUS**
**VTE Prophylaxis#**
Discuss with ID if patient is ineligible or declines remdesivir therapy (see Note 1)

**#VTE Prophylaxis**: Should be considered for pregnant women with mild disease with any of the following risk factors for VTE: prior VTE, age >35 years, BMI > 40 or BMI > 30 with another risk factor for VTE, blood dyscrasias or smoker. **CrCl > 30mL/min:** enoxaparin 40mg subcutaneous injection daily, **CrCl < 30mL/min:** enoxaparin 20mg subcutaneous injection daily.

**Box 2: Definition of not up to date vaccine status:** Unvaccinated **OR** single dose vaccination **OR** less than 2 weeks since primary course of COVID-19 vaccination **OR** less than 7 days since first booster vaccination **OR** ≥ 3 months since primary COVID-19 vaccination course with no booster vaccination. When considering vaccination status take into account time since booster vaccination and current ATAGI recommendation for age. Refer to the Australian Immunisation Handbook for more information.

**Box 3: Dosing Recommendations for Disease-Modifying Treatments of COVID-19**
**Remdesivir:** 200mg IV infusion loading dose day 1 then 100mg IV daily on day 2 and 3. Total 3 day course.

**Note 1:** There is limited evidence for disease modifying therapies in pregnant and breastfeeding women and the decision to treat should be based on risk factors for progressing to severe illness (as listed in Box 1) taking into account the harm benefit ratio for both mother and foetus. Seek advice from ID.

**Box 1: Risk factors for progressing to severe illness**

- Renal impairment (eGFR < 60mL/min)
- Diabetes (requiring medication)
- Obesity (BMI > 40 kg/m$^2$)
- Chronic liver disease (cirrhosis)
- Coronary artery disease
- Heart failure and cardiomyopathies
- Respiratory compromise including: history of chronic bronchitis, cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, moderate-to-severe asthma requiring an inhaled steroid to control symptoms or caused by neurological or musculoskeletal disease
- Neurological conditions e.g. stroke, dementia, demyelinating conditions (inc multiple sclerosis)
- Residential aged care
- Disability with multiple comorbidities and/or frailty
- Past COVID-19 infection episode resulting in hospitalisation
- 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

Please note the following "High risk conditions" are now included in the list of immunocompromised conditions as per PBS criteria

- People with disability with multiple comorbidities and/or frailty
- Down Syndrome
- Cerebral palsy
- Congenital heart disease
- Thalassemia
- Sickle cell disease
- Other haemoglobinopathies not already listed

Health
Central Adelaide

| Title | COVID-19: Medication Management of Mild Illness in the Outpatient Setting |
|---|---|

# 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 < 12 years and <40kg
- Pregnant or breastfeeding
- Solid organ transplant recipients
- Severe liver disease (i.e. Child Pugh Class C)
- 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 | |

* Paxlovid® will increase exposure to these medications – assess if medicine can be safely stopped for 8 days.
^ Paxlovid will decrease efficacy of clopidogrel. Consider risk of thrombotic events before commencing Paxlovid®.
For more information on when medications can be recommenced check University of Liverpool COVID-19 resource page
Note: list of medications is not exhaustive and may change.

**No nirmatrelvir plus ritonavir (Paxlovid®)**

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?**

No

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.

No

**No nirmatrelvir plus ritonavir (Paxlovid®)**

**Medications unlikely to interact or to have a significant interaction with nirmatrelvir plus ritonavir:**

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

**Give nirmatrelvir plus ritonavir (Paxlovid)**

**Nirmatrelvir plus ritonavir (Paxlovid®) dosing**

**eGFR ≥ 60 mL/min:**
300mg nirmatrelvir (2x150mg capsules) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days
**eGFR < 60mL/min:**
150mg nirmatrelvir (1x150mg capsule) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days – use with caution in patients with eGFR < 30ml/min (see drug monograph)

## Disease-modifying treatments for mild COVID-19 illness

### Nirmatrelvir plus Ritonavir (Paxlovid®) [1,7,15,16, 24, 25, 26,31,33, 34, 35]

**Patient consent required (verbal or written)**

Stock not available after hours in CALHN

**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** | • 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 nirmatrelvir. |
| **Indications** | • First line treatment of mild COVID-19 for non-pregnant adults who do NOT require supplemental oxygen and are ≤ 5 days since symptom onset AND:<br>○ Are immunosuppressed (irrespective of vaccination status or age)<br>**OR**<br>○ Have previously experienced COVID-19 infection requiring hospitalisation (irrespective of vaccination status or age)<br>**OR**<br>○ Aged < 50 years (or < 30 years if Aboriginal or Torres Strait Islander) **with** TWO or more risk factors for severe or critical illness (irrespective of vaccination status)<br>**OR**<br>○ Aged ≥ 50 to 69 years with TWO or more risk factors for severe or critical illness (irrespective of vaccination status)<br>**OR**<br>○ Aboriginal or Torres Strait Islander AND aged ≥ 30 years with ONE or more risk factors for severe or critical illness (irrespective of vaccination status)<br>**OR**<br>○ Aged ≥ 70 years regardless of vaccination status or risk factors for progressing to severe or critical illness<br>• **Check for contraindications and drug interactions before prescribing.**<br>• 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** | • Hypersensitivity to nirmatrelvir or ritonavir or any of the excipients listed in the product information.<br>• Children less than 12 years old and weighing < 40kg.<br>• **Pregnancy** – the use of nirmatrelvir plus ritonavir in pregnant patients is not recommended as there is no human data to evaluate the drug-associated risk of adverse developmental outcomes. Women of childbearing age 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.<br>• **Breastfeeding** – limited data. Based on the potential for adverse reactions on the infant, breastfeeding is not recommended during AND for 7 days after treatment.<br>• **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.<br>• **Severe hepatic impairment** – avoid due to insufficient data.<br>• **Solid organ transplant recipients**<br>• **Drug interactions**<br>  ○ 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.<br>  ○ Co-administration of medications which are potent CYP3A4 inducers which can result in significantly reduced plasma concentrations of nirmatrelvir plus ritonavir and could be associated with loss of virologic response and possible resistance. See below for examples. |
| **Precautions** | • Exercise caution in patients with a history of anaphylaxis to other medicines.<br>• **Severe renal impairment** (eGFR < 30 mL/min) – use with caution. Dose recommendations are from the Renal Drug Database and are based on a study from Wales with small numbers of patients with end stage renal disease (ESRD). In this study patients with ESRD taking this dose experienced no serious adverse effects.<br>• **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.<br>• **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** | • 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.<br>• Store at room temperature, less than 25$^{o}$C |
| **Dose** | • **eGFR ≥ 60mL/min/1.73m$^2$**: Nirmatrelvir 300mg (two 150mg tablets) with ritonavir 100mg (one 100mg tablet) taken together orally every 12 hours for 5 days.<br>• **eGFR < 60 mL/min/1.73m$^2$**: Nirmatrelvir 150mg (one 150mg tablet) with ritonavir 100mg (one 100mg tablet) taken together orally every 12 hours for 5 days. See precautions section above for patients with eGFR <30mL/min/1.73m$^2$<br><br>No dose adjustment is required for patients with mild or moderate hepatic impairment. Avoid use in patients with severe hepatic impairment.<br>• 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** | • The blister strips for Paxlovid® contain two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose (morning and night doses are separated within the same blister strip). Therefore, patients with moderate renal impairment should be alerted to the fact that only one tablet of nirmatrelvir should be taken every 12 hours (with the tablet of ritonavir).<br>• Where possible swallow the tablets whole, with or without food. |

| | |
|---|---|
| | • There is little information regarding the safety or efficacy of nirmatrelvir plus ritonavir when tablets are crushed or dispersed, however the following instructions have been provided for those with swallowing difficulties or enteral feeding tubes:<br>○ For patients with swallowing difficulties:<br>1. Disperse the nirmatrevir tablet(s) in water OR if the patient is unable to swallow thin fluids, crush the nirmatrelvir tablet(s) and mix with a spoonful of yoghurt or apple puree.<br>2. Crush the ritonavir tablet and mix with water, or a spoonful of yoghurt or apple puree.<br>○ For patients with enteral feeding tubes:<br>1. Flush the tube with 30mL of water.<br>2. Disperse the nirmatrelvir tablet(s) in 10-20mL of water in an enteral syringe. The tablet(s) will form a milky, light pink dispersion within a few minutes.<br>3. Check carefully that the tablet(s) is completely dispersed and then give via enteral tube.<br>4. Flush tube with 5mL of water.<br>5. Crush the ritonavir tablet and mix with water, then draw into an enteral syringe.<br>6. Give the mixture via enteral tube ensuring all the mixture has been administered.<br>7. Flush the tube with 30mL of water. |
| **Monitoring** | • Baseline creatinine, electrolytes and urea, LFTs and complete blood exam.<br>• Monitor the patient for adverse effects.<br>• 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** | • It may be difficult to distinguish between adverse effects of nirmatrelvir or ritonavir and the signs and symptoms of COVID-19.<br>• 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.<br>• To date the most common adverse reactions reported include:<br>○ altered sense of taste<br>○ headache<br>○ diarrhoea<br>○ vomiting<br>○ hypertension<br>○ myalgia<br>• 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** | • Nirmatrelvir plus ritonavir patient information leaflets 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 UGT enzymes that mediate glucuronidation.<br>• Always check the University of Liverpool COVID-19 resource page or Up-To-Date interaction checker prior to prescribing nirmatrelvir plus ritonavir.<br>• 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, Up-to- |

date interaction checker 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

^ Paxlovid will decrease efficacy of clopidogrel. Consider risk of thrombotic events before commencing Paxlovid.

## Remdesivir[1,4,13, 29,30,32]

**ID approval and patient consent (verbal or written) required**

**For more detailed information on the use of remdesivir in patients with COVID-19 visit the product information available on the TGA website**

| | |
|---|---|
| **Drug Class** | • Antiviral, a nucleotide analogue prodrug that binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription. |

| | |
|---|---|
| **Indications** | • Second line treatment (when nirmatrelvir plus ritonavir is contraindicated or not suitable) of mild COVID-19 for non-pregnant adult patients who do not require supplemental oxygen and are **within 7 days of symptom onset**<br>**AND**<br>• Are immunosuppressed (regardless of vaccination status)<br>**OR**<br>• Have previously experienced COVID-19 infection requiring hospitalisation (irrespective of vaccination status or age)<br>**OR**<br>• Aged 50 to 69 years or ≥ 30 years if Aboriginal and/or Torres Strait Islander irrespective of vaccination status with **ONE** or more risk factors for progressing to severe or critical illness<br>**OR**<br>• Aged ≥ 70 irrespective of vaccination status or risk factors for progressing to severe or critical illness<br>**OR**<br>• Aged < 50 years or < 30 if Aboriginal and/or Torres Strait Islander with **THREE** or more risk factors for progressing to severe or critical illness (irrespective of vaccination status)<br><br>• Treatment of breastfeeding or pregnant patients in their second or third trimester within 7 days of symptom onset and do not require supplemental oxygen AND:<br>• are Immunosuppressed irrespective of vaccine status<br>**OR**<br>• who have reduced immunity to COVID-19 e.g. not vaccinated or do not have an up-to-date vaccine status **AND** who have one or more risk factors for progressing to severe or critical illness. |
| **Contra-indications** | • Known hypersensitivity to any ingredient of remdesivir product or remdesivir metabolites.<br>• Mechanical ventilation for >48 hours at the time of commencement.<br>• Hepatic impairment: ALT ≥ 5 times the upper normal limit (ULN) at baseline.<br>• Patients with evidence of multiorgan failure, including coagulopathy (significant thrombocytopenia), hepatic failure, renal failure or significant cardiomyopathy are not eligible to access remdesivir from the National Medicines Stockpile (NMS). |
| **Precautions** | • Severe Renal impairment[1]: eGFR < 30mL/min/1.73m$^2$<br>○ Remdesivir is formulated with the excipient sulfobutyl betadex sodium (SBECD) which accumulates in renal impairment. For most patients with an eGFR < 30mL/min/1.73m$^2$ the benefit of treatment will outweigh the risks of treatment as the reported toxic doses of SBECD are 50-100 times higher than exposure during a 5-10 day course of remdesivir.<br>○ The Renal Drug Database and FDA have recently updated dosing recommendations for patients with eGFR < 30mL/min/1.73m$^2$ and both state remdesivir can be used in patients with eGFR < 30mL/min/1.73m$^2$ without need for dose adjustment.<br>• Factors where the benefit of remdesivir is uncertain & requires careful consideration before use:<br>○ Presence of an intercurrent illness likely to lead to patient death within one year; |

[1] NOTE: Dose adjustments are based on eGFR (CKD-EPI). For patients with extremes of body size, multiply the eGFR by the patient's body surface area (in m$^2$) and divide by 1.73 m$^2$

| | |
|---|---|
| | ○ Advanced age with limitations on activities of daily living;<br>○ Need for more than a 5 day treatment course (not available via NMS). |
| **Drug Interactions** | • Drug-drug interaction trials of remdesivir and other concomitant medications have not been conducted in humans. Remdesivir is a substrate for several drug metabolising enzymes however clinical relevance of these interactions has not been established.<br>• Use with hydroxychloroquine or chloroquine is not recommended as it may reduce antiviral activity of remdesivir.<br>• For detailed information regarding drug interactions with remdesivir please check the University of Liverpool COVID-19 resource page. |
| **Preparation** | • There are 2 preparations available in Australia via the NMS:<br>○ Powder for injection<br>▪ 100 mg sterile, preservative-free, white to off-white to yellow lyophilised powder vial.<br>▪ Requires storage below 30°C.<br>▪ Contains sulfobutyl betadex sodium (SBECD 3 g), hydrochloric acid & sodium hydroxide.<br>○ Concentrated solution vial<br>▪ 100 mg/20 mL concentrate solution (clear colourless to yellow) vial; sterile preservative-free.<br>▪ Requires refrigerated storage at 2–8°C.<br>▪ Stable for up to 12 hours at room temperature (20–25°C) prior to dilution.<br>▪ Contains sulfobutyl betadex sodium (SBECD 6 g), hydrochloric acid & sodium hydroxide.<br>▪ Concentrated solution not recommended in children < 12 years of age or adolescents weighing <40kg. |
| **Dose** | • **Mild illness:** 200mg via IV infusion on day 1, then 100mg IV daily for a further 2 days (total 3 days treatment).<br>• **Moderate to critical illness:** 200mg via IV infusion on day 1, then 100mg IV daily for a further 4 days (total 5 days treatment only per NMS). |
| **Administration** | • There are different formulations of remdesivir available via the NMS and administration instructions may vary.<br>• For administration details refer to the Australian Injectables Drugs Handbook. |
| **Monitoring** | • As experience with remdesivir at these doses and for this duration is limited, patients should have appropriate clinical and laboratory monitoring including:<br>○ Baseline and day 1 and 3 creatinine, electrolytes, urea, LFTs and complete blood exam. If patient is having haemodialysis then bloods can be completed at next dialysis sessions instead of day 1 and 3.<br>▪ Discontinue remdesivir if:<br>• eGFR < 30mL/min/$m^2$ (contact ID to discuss risk vs benefit)<br>• ALT ≥ 5 times ULN during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times ULN), OR<br>• ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.<br>○ Perform baseline and DAILY coagulation profile testing, including prothrombin time.<br>○ Heart rate. |

| | |
|---|---|
| | ○ Observe for infusion-related reactions. If present, immediately discontinue administration of remdesivir and initiate supportive therapy if required. |
| **Adverse Effects** | • As experience with remdesivir at these doses and for this duration is limited patients it is important to document and report all suspected adverse effects. To date, the following adverse effects have been observed:<br>○ Very common (>10%): graded elevations in ALT, AST and bilirubin.<br>○ Common (>1%): prolonged prothrombin time, gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea), headache, rash.<br>○ Rare (<0.1%): hypersensitivity reactions (anaphylactic reactions are rare but are a medical emergency; stop the infusion and begin treatment immediately).<br>• Infusion-related reactions may include hypotension, nausea, vomiting, diaphoresis, shivering.<br>• Post-marketing adverse effects reported include bradycardia (including severe bradycardia and sinus bradycardia), cardiac failure and hypotension.<br>• 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 and consent forms** | • CALHN Remdesivir Consumer Information Leaflets can be found here.<br>• Remdesivir patient information leaflets are also available via the NSW Clinical Excellence Commission. |

| **Molnupiravir (Lagevrio®) [1,7,14,17,20]**<br>**Patient consent (verbal or written) required**<br>Stock not available after hours<br>**For more detailed information on the use of Molnupiravir in patients with COVID-19 visit the product information available on the TGA website** | |
|---|---|
| **Drug Class** | • Antiviral pro-drug, which once metabolised to an active ribonucleoside triphosphate (NHC-TP), is incorporated into SARS-CoV-2 viral RNA resulting in an accumulation of transcribed mutations with each viral replication cycle, thus inhibiting further replication. |
| **Indications** | The National Clinical Evidence Taskforce recently recommended against routine use of molnupiravir, except in specific circumstances and where all other treatment options are contraindicated OR inappropriate, based on the results of the PANORAMIC Trial. The median age of patients in the PANORAMIC trial was 56 years (younger than target treatment groups in Australia) and a reduction in time to recovery was shown for all patients and trend to reduced hospitalisation/death in patients aged ≥ 80 years. The AMS Committee note recent Victorian data which showed a reduction in hospitalisation and death in patients aged ≥ 70 years who received molnupiravir. Molnupiravir should continue to be considered when nirmatrelvir/ritonavir and/or remdesivir are contraindicated, inappropriate or inaccessible.<br><br>Consider risk versus benefits of molnupiravir as limited evidence in patients <70 years. For patients aged < 70 years who are contraindicated from taking nirmatrelvir/ritonavir and/or remdesivir, only prescribe molnupiravir if benefits outweigh risks AND appropriate reproductive counselling can be provided.<br><br>• Second or third line treatment of mild COVID-19 for non-pregnant adults where nirmatrelvir plus ritonavir AND remdesivir are not available or contraindicated and benefits |

| | |
|---|---|
| | of treatment outweigh risks and appropriate reproductive counselling is provided. Patients must have symptom onset of no more than 5 days, not require supplemental oxygen and be:<br>○ Immunosuppressed (irrespective of vaccine status)<br>**OR**<br>○ Aged ≥ 70 years irrespective of vaccination status or risk factors for progressing to severe or critical illness<br>**OR**<br>○ Aged 50 to 69 years PLUS ≥ 2 risk factors for progressing to severe or critical illness (irrespective of vaccination status) OR a past COVID-19 infection requiring hospitalisation<br>**OR**<br>○ Aboriginal or Torres Strait Islander and aged ≥ 30 years PLUS ≥ 1 risk factor for progressing to severe or critical illness (irrespective of vaccination status)<br>**OR**<br>○ Aged < 50 years or < 30 years if Aboriginal or Torres Strait Islander **PLUS** ≥ 3 risk factors for progressing to severe or critical illness (non PBS).<br><br>• 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** | • Hypersensitivity to molnupiravir or any of the excipients in the product.<br>• Children less than 18 years old.<br>• **Pregnancy** – the use of molnupiravir in pregnant patients is **not recommended** due to potential risk of reduced foetal growth and development.<br>• **Breastfeeding** – it is unknown whether molnupiravir is present in human breastmilk, affects breastmilk production, or has an effect on the breastfed infant. Based on the potential for adverse reactions on the infant, breastfeeding is **not recommended** during AND for 4 days after treatment.<br>• **Contraception -** Prescribers should consider a pregnancy test prior to commencement of therapy. Advise women of childbearing potential to use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir. Advise men who are sexually active with a partner of childbearing potential to use an adequate form of contraception during and 3 months after treatment with molnupiravir. |
| **Precautions** | • Exercise caution in patients with a history of anaphylaxis to other medicines.<br>• **Renal Impairment -** Patients with eGFR < 30mL/min and patients on dialysis were excluded from the Phase 3 MOVe-OUT trial. Molnupiravir is a prodrug hydrolysed to NHC. The fraction of dose excreted as NHC was ≤ 3% therefore renal impairment is not expected to have a significant effect on NHC exposure.<br>• **Hepatic impairment –** the pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with hepatic impairment. Hepatic elimination is not expected to be a major route of NHC elimination. |
| **Drug Interactions** | • No formal interaction studies have been conducted with molnupiravir.<br>• The metabolite of molnupiravir is not a substrate of major drug metabolising enzymes or transporters. Neither molnupiravir nor its substrate are inhibitors or inducers of major drug metabolising enzymes or transporters.<br>• While the potential for drug interactions with molnupiravir are considered unlikely, as this is a new drug, continue to check the University of Liverpool COVID-19 resource page. |

| | |
|---|---|
| **Presentation and storage** | • Available as 200mg capsules supplied as a bottle of 40 capsules.<br>• Store at room temperature, less than 30°C |
| **Dose** | • 800mg (4 x 200mg capsules) orally 12-hourly for 5 days.<br>• No dose adjustment is required for renal or hepatic impairment or the elderly (see precautions above).<br>• If the patient misses a dose of molnupiravir within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If a patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose. |
| **Administration** | • Capsules can be taken with or without food.<br>• Administration of molnupiravir via an oral solution has not been evaluated in clinical trials however the following advice has been provided for patients with swallowing difficulties and or for administration via an enteric tube.<br>• Preparation of the solution:<br>  ○ Open FOUR (4) capsules and transfer contents into an oral syringe. Discard empty capsule shells.<br>  ○ Add approximately 40 mL of water to the oral syringe.<br>  ○ Mix/stir the capsule contents and water for 3 minutes.<br>  1. Insoluble capsule contents may not dissolve completely.<br>  2. Reconstituted solutions prepared according to directions may have visible undissolved particulates and are acceptable for oral administration.<br>  ○ Administration should occur as soon as possible after the preparation and no later than 2 hours after the preparation.<br>• For administration via enteral tube:<br>  ○ Prior to administration redisperse the suspension by mixing or stirring the oral syringe for 1 minute prior to administration.<br>  ○ Flush enteral tube with 5 mL of water prior to administration.<br>  ○ Administer entire volume from the administration syringe.<br>  ○ Flush tube with 5 mL of water TWICE (10 mL total) after administration of the suspension. |
| **Handling** | • Occupational exposure to non-intact tablets may be harmful. Staff who are actively trying to conceive or who are pregnant or breastfeeding should not prepare or handle a dispersed dose.<br>• For all other staff, use standard Personal Protective Equipment (PPE) if preparation or administration of a dispersed tablet is required. |
| **Monitoring** | • Baseline creatinine, electrolytes and urea, LFTs and complete blood exam.<br>• Monitor the patient for adverse effects.<br>• 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** | • It may be difficult to distinguish between adverse effects of molnupiravir and the signs and symptoms of COVID-19.<br>• As a new medication, adverse reactions to molnupiravir continue to be investigated. Refer to the product information for a complete list of possible adverse effects. To date reactions include:<br>  ○ Common (>1%): diarrhoea, nausea, dizziness, headache<br>  ○ Uncommon (0.1-1%): rash, urticaria<br>• 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 and consent forms** | • Molnupiravir patient information leaflets can be found here. |

## 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 |
| MDI | Metered dose inhaler |
| NMS | National Medical Stockpile |
| NYHA | New York Heart Association |

## APPENDICES

Appendix 1: Definition of COVID-19 disease severity for adults

## 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-CPA04038)
- 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

## REFERENCES

1. National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. https://covid19evidence.net.au/#living-guidelines . Published 2022 (v69.0). Accessed Dec 2022.
2. NSW Therapeutic Advisory Group Inc. COVID-19 Resources: Medicine use in the treatment of COVID-19. https://www.nswtag.org.au/covid-19-medicines-resources/. Published 2021. Accessed 2021 October
3. Therapeutic Goods Administration – Xevudy (Sotrovimab). TGA; 2021. https://www.tga.gov.au/auspar/auspar-sotrovimab. Published 20th August 2021, Accessed October 2021
4. Society of Hospital Pharmacists of Australia. Australian Injectable Drugs Handbook (online). In:8th ed. Collingwood: Society of Hospital Pharmacists of Australia; 2021: https://aidh.hcn.com.au/browse/s/sotrovimab. Accessed October 2021
5. National Institutes of Health. Corticosteroids 2021. https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/corticosteroids/#:~:text=Patients%20with%20severe%20COVID%2D19,or%20mitigate%20these%20deleterious%20effects. Accessed October 2021
6. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. 2020. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed October 2021
7. Liverpool Drug Interactions Group. Interaction Checker and Prescriber Resources. https://www.covid19-druginteractions.org/checker. Accessed Dec 2022
8. Australian Medicines Handbook Pty Ltd; 2021. https://amhonline.amh.net.au/. Accessed October 2021
9. World Health Organisation. Therapeutics and COVID-19: Living Guideline. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3. Accessed October 2021
10. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. CDC. https://www.cdc.gov/vaccines/covid-19/downloads/clinical-considerations-slides-for-hcp.pptx Updated 2021 September. Accessed 2021 October 2021.
11. National Asthma Council of Australia. https://www.nationalasthma.org.au/. Accessed Nov 2021
12. Clinical Excellence Commission. Medication Safety Updates. https://www.cec.health.nsw.gov.au/keep-patients-safe/medication-safety/medicine-updates Accessed March 2022
13. Bernal AJ et al. Molnupiravir for oral treatment of Covid-19 in non-hospitalised patients (MOVe-OUT). *NEJM.* December 16, 2021. DOI: 10.1056/NEJMoa2116044
14. Evaluation of Protease Inhibition for COVID-19 in High-Risk patients (EPIC-HR study). Study of oral PF-07321332/ritonavir compared with placebo in non-hospitalised high risk adults with COVID-19. https://clinicaltrials.gov/ct2/show/NCT04960202. Accessed 1/2/2022.
15. Therapeutic Goods Administration – Paxlovid TGA; 2022. https://www.tga.gov.au/apm-summary/paxlovid Published 21st Jan 2022, Feb 2022
16. Therapeutic Goods Administration – Molnupiravir TGA; 2022. https://www.tga.gov.au/apm-summary/molnupiravir. Published 21st Jan 2022, Feb 2022
17. UK Interim Clinical Commissioning Policy: therapies for symptomatic non-hospitalised patients with COVID-19. Version 1. Published 27th Jan 2022
18. Centres for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers. CDC. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers (cdc.gov). Updated 14th Oct 2021. Accessed Feb 2022 https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
19. Merck Sharp & Dohme Medicines Information response Re: Administration of molnupiravir in patients who cannot swallow. Feb 11 2022

20. Australian Technical Advisory Group on Immunisation (ATAGI). ATAGI statement on defining 'up-to-date' status for COVID-19 vaccination. https://www.health.gov.au/news/atagi-statement-on-defining-up-to-date-status-for-covid-19-vaccination. Published Feb 10 2022. Accessed July 2022
21. Australian Technical Advisory Group on Immunisation (ATAGI). ATAGI Recommendations on the use of a third primary dose of COVID-19 vaccine in individuals who are severely immunocompromised. https://www.health.gov.au/sites/default/files/documents/2022/03/atagi-recommendations-on-the-use-of-a-third-primary-dose-of-covid-19-vaccine-in-individuals-who-are-severely-immunocompromised.pdf Published 25 March 2022. Accessed April 2022
22. Takashita E et al. Efficacy of antiviral agents against the SARS-CoV-2 Omicron subvariant BA.2. NEJM letter. Published March 9 2022.
23. The Pharmaceutical Benefits Scheme. Nirmatrelvir & Ritonavir, Molnupiravir. Pharmaceutical Benefits Scheme (PBS) |. Accessed March 2024 https://www.pbs.gov.au/medicine/item/12996B
24. Nirmatrelvir plus ritonavir prescribing guideline. Queensland Department of Health. July 2022. Accessed September 2022 https://www.health.qld.gov.au/__data/assets/pdf_file/0021/1142076/nirmatrelvir-prescribing-guideline.pdf
25. Hiremath S, McGuinty M, et al. Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD. Clinical Journal of The American Society of Nephrology. 2022, 17:1247-1250.
26. Brown PA, McGuinty M, Argyropoulos C, Clark EG, et al. Early experience with modified dose nirmatrelvir/ritonavir in dialysis patients with coronavirus disease-2019. medRxiv.2022:2022.05.18.22275234
27. Australian Don't Rush to Crush. The Society of Hospital Pharmacists of Australia. Accessed via MIMS Online. Accessed Dec 2022
28. Australian Immunisation Handbook: COVID-19. https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/covid-19. Accessed March 2024
29. Food and Drug Administration. Prescribing Information – Remdesivir https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/214787s019lbl.pdf. Accessed April 2024
30. The Renal Drug Database. The UK Renal Pharmacy Group. Remdesivir. Accessed April 2024
31. The Renal Drug Database. The UK Renal Pharmacy Group. Nirmatrelvir/ritonavir. Accessed April 2024
32. Sorgel F, Malin JJ, et al. Pharmacokinetics of remdesivir in a Covid-19 patient with end stage renal disease on intermittent haemodialysis. Journal of Antimicrobial Chemotherapy 2020 doi: 10.1093/jac/dkaa500
33. Cho W, Harden D et al. Oral antiviral therapies for COVID-19 in patients with advanced chronic kidney disease or kidney failure. Nephrology, Dialysis, Transplantation. 2023. 38(8) 1912-1914. https://doi.org/10.1093/ndt/gfad058
34. Chan G, Lui G et al. Safety profile and clinical and virological outcomes of nirmatrelvir-ritonavir treatment in patients with advanced chronic kidney disease and Coronavirus Disease 2019. Clinical Infectious Diseases. 2023. 77 (15 November) page 1406-1412.
35. Lingscheid T, Kinzig M, Krüger A, Müller N, Bölke G, Tober-Lau P, et al. Pharmacokinetics of Nirmatrelvir and Ritonavir in COVID-19 Patients with End-Stage Renal Disease on Intermittent Hemodialysis. Antimicrob Agents Chemother. 2022 Nov; 66(11): e01229-22

## Appendix 1 – Definition of COVID-19 disease severity for adults[1]

| | |
|---|---|
| **Mild illness (outpatient or inpatients admitted with another condition)** | Adults not presenting any clinical features suggestive of moderate or severe disease or a complicated course of illness.<br>• Characteristics:<br>  ○ no symptoms; or<br>  ○ mild upper respiratory tract symptoms; or<br>  ○ cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation<br>  ○ Oxygen saturations >95% on room air |
| **Moderate illness (ward based care)** | Stable patient presenting with respiratory and/or systemic signs or symptoms. Able to maintain oxygen saturation above 92% at rest (or above 90% for patients with chronic lung disease) with up to 4L/min oxygen via nasal prongs.<br>• Characteristics:<br>  ○ fatigue, fever > 38ºC or persistent cough<br>  ○ clinical or radiological signs of lung involvement<br>  ○ no clinical or laboratory indicators of clinical severity or respiratory impairment |
| **Severe illness (specialised ward or ICU)** | Adult patients meeting any of the following criteria:<br>• respiratory rate ≥ 30 breaths/min<br>• oxygen saturation ≤ 92% at a rest state on ≥ 4L/min oxygen via nasal prongs<br>• arterial partial pressure of oxygen ($PaO_2$) / inspired oxygen fraction ($FiO_2$) ≤ 300 |
| **Critical illness (ICU)** | Adult patients meeting any of the following criteria:<br>• Respiratory failure as defined by:<br>  ○ severe respiratory failure ($PaO_2/FiO_2$ < 200), respiratory distress or acute respiratory distress syndrome<br>  ○ deterioration despite advanced forms of respiratory support (non-invasive ventilation, high flow nasal oxygen) OR requiring mechanical ventilation<br>**OR**<br>• Other signs of significant deterioration:<br>  ○ hypotension or shock<br>  ○ impairment of consciousness<br>  ○ other organ failure |

**End of Appendix 1**