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: 19/07/2023

Version 5.0

Approval date: 19/07/2023

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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			
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Oversight committee	CALHN Drugs and Therapeutics Committee			
Committee endorsement	19 July 2023			
Sponsor	A/Prof David Shaw – Head of Unit, Infectious Diseases/IPCU, CALHN			
Sponsor approval	19 July 2023			
Priority Care Committee (PCC)	PCC: National Standard 4 Medication Safety			
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Monitoring/audit	☒ Scheduled for audit		☐ Not scheduled for audit	
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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, sotrovimab, molnupiravir, nirmatrelvir, ritonavir, remdesivir, mild.			

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
5.0	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

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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 Care Centre.
- 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 please 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 11)

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.

Supplies of medications from the National Medical Stockpile (NMS) can vary according to outbreaks and demand and in the setting of limited supply certain risk factors or patients with greater than 1 risk factor may be prioritised for treatment of mild disease.

Classification of Immunosuppressed Patients

Immunosuppressed patients are not expected to mount an adequate immune response to COVID-19 vaccination or a COVID-19 infection due to their underlying conditions, regardless of their vaccine status.

Medical conditions associated with reduced immune response	

Haematological disease and stem cell transplant recipients	• Haematopoietic stem cell transplant (HSCT) recipients in the last 24 months (allogenic or autologous)
	• Active graft vs host disease regardless of time from transplant (including HSCT for non-malignant diseases)
	• Active haematological neoplasms including: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders including individuals who have received:
	  ○ Chimaeric antigen receptor (CAR)-T therapy within the last 2 years OR
	  ○ Whole body radiotherapy within the last 6 months OR
	  ○ Systemic anti-cancer treatment (SACT) within the last 12 months except:
	  ○ patients with chronic phase chronic myeloid leukaemia (CML) in molecular response OR
	  ○ first or second line tyrosine kinase inhibitors (TKI) – see medications section below for more information
	• Individuals with non-malignant haematological disorder (e.g. aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (see medication section below) within the last 12 months

Patients with non-haematological malignancies	Any metastatic cancer OR solid cancers where patients have received chemotherapy or whole body radiotherapy within the last 6 months
Solid organ transplant	All solid organ transplant patients receiving immunosuppressive therapy
Primary or acquired immune deficiencies	• Primary immunodeficiency associated with impaired type I interferon signalling • Good's syndrome (thymoma plus B-cell deficiency) • X-linked agammaglobulinaemia (and other primary agammaglobulinaemias) • Any patient with a secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy • Common variable immunodeficiency (CVID) • Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig) • Hyper-IgM syndromes • Severe Combined Immunodeficiency (SCID) syndromes • Autoimmune polyglandular syndromes /autoimmunepolyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome) • Aplastic anaemia on active therapy • Advanced or untreated HIV with CD4 counts < 250/μL or those with a higher CD4 count unable to be established on effective antiretroviral therapy • Other primary or acquired immune deficiencies not listed – discuss with usual treating specialist to determine immune deficiency and eligibility
High risk conditions considered immunosuppressive 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

NOTE asplenic or hyposplenic patients are not classified as immunosuppressed

Medications associated with a reduced immune response to COVID-19 vaccination For all medications listed, treatment within the last 3 months is considered immunosuppressive (unless otherwise stated)	
Corticosteroids	High dose corticosteroid treatment equivalent to ≥ 20mg/day of prednisone for ≥ 14 days in a month, or pulse corticosteroid therapy.
Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDS)	• mycophenolate • methotrexate • leflunomide • azathioprine • 6-mercaptopurine (≥ 0.5mg/kg/day), PBS eligibility (>1.5mg/kg/day)* • alkylating agents (e.g. cyclophosphamide, chlorambucil) • systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus).
Rituximab	Any patient, with a condition not already listed, who has received rituximab within the last 12 months
Biologic and targeted therapies including	Anti-CD20 antibodies within 12 months • obintuzumab, ocrelizumab, ofatumumab BTK inhibitors within 6 months (PBS eligible within 3 months)* • ibrutinib, acalabrutinib, zanubrutinib JAK inhibitors (PBS eligible within 3 months)* • tofacitinib, baricitinib, ruxolitinib, upadacitinib Sphingosine 1-phosphate receptor modulators (PBS eligible within 3 months)* • fingolimod, siponimod Anti-CD52 antibodies within 6 months (PBS eligible within 3 months)* • Alemtuzumab Anti-complement antibodies (PBS eligible within 3 months)* • Eculizumab Anti-thymocyte globulin (ATG) (PBS eligible within 3 months)* • anti-thymocyte globulin (e.g. ATGAM®, Thymoglobuline®, ATG-Grafalon®) Pyrimidine and purine synthesis inhibitors (not included in PBS eligible medications)* • teriflunamide, cladribine Other agents • PBS eligible with treatment within 3 months: abatacept • Not included in PBS eligible medications*: belimumab, blinatumomab, dimethyl fumarate, venetoclax, daratumumab
Multiple immunosuppressants or combination immunosuppression	Combination therapy where the cumulative effect is severely immunosuppressive*

* For medications listed above but not eligible per PBS criteria (i.e. medication not included in PBS criteria, time since administration > 3 months but < 12 months for anti-CD20 antibodies or < 6 months for BTK inhibitors and anti-CD52 antibodies or patient on lower dose than PBS eligibility) antiviral medications may be prescribed non PBS and dispensed by public hospital pharmacy.

Medications not associated with a reduced response to COVID-19 vaccination

The following therapies, when **not** given in combination with other immunosuppressive therapies, are likely to have a minimal effect on COVID-19 vaccine response.

- Anti-TNF-α antibodies (e.g. infliximab, adalimumab, etanercept, golimumab, certolizumab)
- Anti-IL1 antibodies (e.g. anakinra)
- Anti-IL6 antibodies (e.g. siltuximab, tocilizumab and sarilumab)
- Anti-IL17 antibodies (e.g. apremilast, secukinumab, ixekizumab)
- Anti-IL4 antibodies (e.g. dupilumab)
- Anti-IL23 antibodies (e.g. guselkumab, risankizumab, tildrakizumab, ustekinumab)
- Immune checkpoint inhibitors (e.g. atezolizumab, durvalamab, ipilimumab, nivolumab, pembrolizumab)
- Integrin receptor inhibitors (e.g. natazilumab, vedolizumab)
- Interferons
- Glatiramer
- VEGF, EGFR and HER2 blockers (e.g. cetuximab, panitumumab, pertuzumab, traztuzumab, bevacizumab)

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COVID-19 treatment recommendations for mild illness in non pregnant adults (see page 11 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 8)

- **Aged ≥ 70 years irrespective of risk factors OR**
- **Aged ≥ 50 to 69 years with ≥ 1 risk factor** (see page 9)

Aboriginal or Torres Strait Islander Aged ≥ 30 years AND ≥ 1 risk factor (see page 10)

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 CCC 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 10)

1 or 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

Symptom onset ≤ 7 days

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

Second line:
Symptom onset ≤ 7 days Remdesivir
Via Referral to CCC 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 recommended for patients who had symptom onset > 7 days earlier and those considered at low risk of progressive 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

βConsider 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.

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 cost to the patient if obtained in the community

COVID-19 treatment recommendations for mild illness in adults – Immunosuppressed Patients OR Patients with previous COVID-19 infection requiring hospitalisation

Immunosuppressed 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 11)

First Line →

If **NO** contraindication (e.g. eGFR < 30 mL/min, severe hepatic impairment, solid organ transplant recipients) (see page 12)
and ≤ 5 days since symptom onset

Nirmatrelvir plus Ritonavir (via PBS)

Second Line →

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

Remdesivir
(Referral to CCC 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)

Immunosuppressive conditions include: haematologic neoplasms, solid organ transplant recipients on immunosuppressive therapy, or stem cell transplant recipients within 24 months of transplant, primary or acquired immunodeficiency or patients who have received rituximab within the last 12 months or medications/therapies listed on page 6 within the last 3-12 months.
Other conditions now included on PBS as immunosuppressed: people with disability with multiple/significant comorbidities and/or frailty, Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease, other haemoglobinopathies not already listed

Dosing Recommendations for Disease-Modifying Treatments of COVID-19
Nirmatrelvir plus ritonavir: **eGFR > 60 mL/min:** 300mg nirmatrelvir (2x150mg capsules) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days. **eGFR ≥ 30 to < 60mL/min**: 150mg nirmatrelvir (1x150mg capsule) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days. **eGFR < 30 mL/min:** Not recommended, see drug monograph for patients on dialysis
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)

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 11)

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 8) otherwise prescribe as below.

Irrespective of vaccination status

Aged ≥ 70 years (regardless of risk factors)

OR

Aged ≥ 50 to 69 years PLUS ≥ 1 risk factor (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 CCC or via SA Health referral webpage)

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

Molnupiravir (via PBS)

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

NOTE: Provide supportive care only to 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 cost to the patient if obtained in the community

Box 2: Dosing Recommendations for Disease-Modifying Treatments of COVID-19

Nirmatrelvir plus ritonavir: **eGFR > 60 mL/min:** 300mg nirmatrelvir (2x150mg capsules) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days. **eGFR ≥ 30 to < 60mL/min**: 150mg nirmatrelvir (1x150mg capsule) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days. **eGFR < 30 mL/min:** not recommended, for patients on dialysis 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 medications)
- 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

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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 11)

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

1 or 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

NOTE: Provide supportive care only to patients who are at **low risk of progressing to severe illness** (i.e. unvaccinated or partially vaccinated) with no risk factors for progressing to severe illness (Box 1) and patients who have mild disease symptoms and are > 7 days since symptom onset

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.

Box 3: Dosing Recommendations for Disease-Modifying Treatments of COVID-19
Nirmatrelvir plus ritonavir: **eGFR > 60 mL/min:** 300mg nirmatrelvir (2x150mg capsules) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days. **eGFR ≥ 30 to < 60mL/min**: 150mg nirmatrelvir (1x150mg capsule) + 100mg ritonavir (1x100mg capsule) twice daily for 5 days. **eGFR < 30 mL/min:** not recommended, for patients on dialysis see drug monograph
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. 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 medications)
- 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 cost to the patient if obtained in the community

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

Pregnant Women

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 CCC 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 also 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 ATAGI for more information on booster doses and definition of up to date vaccine status.

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. **If eGFR < 30mL/min and/or on dialysis–** discuss with ID or clinical pharmacy, Infectious Diseases or Renal (see drug monograph for more detail)

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 fetus. Seek advice from ID.

Box 1: Risk factors for progressing to severe illness

- Renal impairment (eGFR < 60mL/min)
- Diabetes (requiring medications)
- 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

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 or 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

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

Disease-modifying treatments for mild COVID-19 illness

Nirmatrelvir plus Ritonavir (Paxlovid®) [1,7,15,16, 24, 25, 26]

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 the 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: ○ Are immunosuppressed (regardless of vaccination status or age) **OR** ○ Have previously experienced COVID-19 infection requiring hospitalisation (regardless of vaccination status or age) **OR** ○ Aged < 50 years (or < 30 years if Aboriginal or Torres Strait Islander) **with** ONE or more risk factors for severe or critical illness (regardless of vaccination status) **OR** ○ Aged ≥ 50 to 69 years with ONE or more risk factors for severe or critical illness (regardless of vaccination status) **OR** ○ Aboriginal or Torres Strait Islander AND aged ≥ 30 years with ONE or more risk factors for severe or critical illness (regardless of vaccination status) **OR** ○ Aged ≥ 70 years regardless of vaccination status or risk factors for progressing to 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	• Hypersensitivity to nirmatrelvir or ritonavir or any of the excipients listed in the product information. • Children less than 12 years old and weighing < 40kg • **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 hepatic impairment** – avoid due to insufficient data.
	• **Solid organ transplant recipients**
	• **Drug interactions**
	  ○ 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	• Exercise caution in patients with a history of anaphylaxis to other medicines. • **Severe renal impairment** (eGFR < 30 mL/min) – generally avoid due to insufficient data. ○ Consider using in patients on haemodialysis only under the guidance of the patient's usual renal team and provided adjustments to the nirmatrelvir/ritonavir packaging can be made, appropriate counselling provided and consent obtained (use in patients with an eGFR < 30 mL/min is currently contraindicated by the TGA). The decision to prescribe to patients on dialysis should always be made in conjunction with the renal team. • **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	• 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^{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 • **eGFR 30-60 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 • **eGFR < 30 mL/min/1.73m^2**: Not recommended – insufficient data • **Dialysis:** Day 1: Nirmatrelvir 300mg (two 150mg tablets) with ritonavir 100mg (one 100mg tablet) taken together orally together ONCE only. Day 2-5: nirmatrelvir 150mg (one 150mg tablet) with ritonavir 100mg (one 100mg tablet) taken together orally ONCE daily. Dose after dialysis on dialysis days. No dose adjustment is required for patients with mild or moderate hepatic impairment. Avoid using in patients with severe hepatic impairment. • 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 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. • 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: ○ For patients with swallowing difficulties: 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 2. Crush the ritonavir tablet and mix with water, or a spoonful of yoghurt or apple puree ○ For patients with enteral feeding tubes: 1. Flush the tube with 30mL of water 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 3. Check carefully that the tablet(s) is completely dispersed and then give via enteral tube 4. Flush tube with 5mL of water 5. Crush the ritonavir tablet and mix with water, then draw into an enteral syringe 6. Give the mixture via enteral tube ensuring all the mixture has been administered 7. Flush the tube with 30mL of water
Monitoring	• 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	• 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: ○ 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	• Nirmatrelvir or 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 UGTs (mediate glucuronidation).
- Always check the University of Liverpool COVID-19 resource page or Up-To-Date interaction checker 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, 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] **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** **AND** • are immunosuppressed (regardless of vaccination status) **OR** • Have previously experienced COVID-19 infection requiring hospitalisation (regardless of vaccination status or age) **OR** • 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 **OR** • Aged ≥ 70 regardless of vaccination status or risk factors for progressing to severe or critical illness **OR** • 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 (regardless of vaccination status) • Treatment of breastfeeding or pregnant women in their second or third trimester within 7 days of symptom onset and do not require supplemental oxygen AND: • are Immunosuppressed irrespective of vaccine status **OR** • 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. • Mechanical ventilation for >48 hours at the time of commencement • Hepatic impairment: ALT ≥ 5 times the upper normal limit (ULN) at baseline • 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

Precautions	• Renal impairment[1]: eGFR < 30mL/min/1.73m^2
	  ○ Formulated with the excipient sulfobutyl betadex sodium (SBECD) which accumulates in renal impairment
	  ○ For patients on dialysis please seek specialist advice as SBECD is cleared to varying degrees depending on the type of dialysis
	  ○ For most patients with an eGFR < 30mL/min/1.73m^2 the benefit of treatment will outweigh the risks of treatment however the decision to treat and possible additional monitoring requirements should be discussed with Clinical Pharmacy, Infectious Diseases or Renal.
	• Factors where the benefit of remdesivir is uncertain & requires careful consideration before use:
	  ○ Presence of an intercurrent illness likely to lead to the patient's death within one year;
	  ○ Advanced age with limitations on activities of daily living;
	  ○ 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 • Use with hydroxychloroquine or chloroquine is not recommended as it may result in reduced antiviral activity of remdesivir • 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
	  ○ Powder for Injection
	  ▪ 100 mg sterile, preservative-free, white to off-white to yellow lyophilised powder vial.
	  ▪ Requires storage below 30°C.
	  ▪ Contains sulfobutyl betadex sodium (SBECD 3 g), hydrochloric acid & sodium hydroxide.
	  ○ Concentrated solution vial
	  ▪ 100 mg/20 mL concentrate solution (clear colourless to yellow) vial; sterile preservative-free.
	  ▪ Requires refrigerated storage at 2–8°C.
	  ▪ Stable for up to 12 hours at room temperature (20–25°C) prior to dilution.
	  ▪ Contains sulfobutyl betadex sodium (SBECD 6 g), hydrochloric acid & sodium hydroxide.
	  ▪ Concentrated solution not recommended in children < 12 years of age or adolescents weighing <40kg

Dose	• **Mild illness:** 200mg via intravenous infusion on day 1, then 100mg IV daily for a further 2 days (total 3 days treatment) • **Moderate to critical illness:** 200mg via intravenous 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 National Medicines Stockpile and administration instructions may vary.

[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

	• For administration details please refer either to the Australian Injectables Drugs Handbook and the NSW Therapeutic Advisory Group page on remdesivir.
Monitoring	• As experience with remdesivir at these doses and for this duration is limited patients should have appropriate clinical and laboratory monitoring including: ○ 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. ▪ Discontinue remdesivir if: • eGFR < 30mL/min/m^2 (contact ID to discuss risk vs benefit) • ALT ≥ 5 times ULN during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times ULN) OR • ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR. ○ Perform baseline and DAILY coagulation profile testing, including prothrombin time ○ 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: ○ Very common (>10%): graded elevations in ALT, AST and bilirubin ○ Common (>1%): prolonged prothrombin time, gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea), headache, rash ○ Rare (<0.1%): hypersensitivity reactions (anaphylactic reactions are rare but are a medical emergency; stop the infusion and begin treatment immediately) • Infusion-related reactions may include hypotension, nausea, vomiting, diaphoresis, shivering • Post-marketing adverse effects reported include bradycardia (including severe bradycardia and sinus bradycardia), cardiac failure and hypotension • 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 • Remdesivir patient information leaflets are also available via the NSW Clinical Excellence Commission

Molnupiravir (Lagevrio®) [1,7,14,17,20]

Patient consent (verbal or written) required

Stock not available after hours

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. 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. • 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 and not require supplemental oxygen and be: ○ Immunosuppressed irrespective of vaccine status **OR** ○ Aged ≥ 70 years irrespective of vaccination status or risk factors for progressing to severe or critical illness **OR** ○ Aged ≥ 50 years or PLUS ≥ 1 risk factors for progressing to severe or critical illness (irrespective of vaccination status). **OR** ○ Aboriginal or Torres Strait Islander and aged ≥ 30 years PLUS ≥ 1 risk factor for progressing to severe or critical illness (irrespective of vaccination status) **OR** ○ Aged < 50 years or < 30 years if Aboriginal or Torres Strait Islander **PLUS** ≥ 1 risk factors) for progressing to severe or critical illness. • 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. • Children less than 18 years old • **Pregnancy** – the use of molnupiravir in pregnant women is **not recommended** due to potential risk of reduced foetal growth and development • **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 • **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. • **Renal Impairment -** Patients with eGFR < 30 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. • **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 • 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. • 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. • Store at room temperature, less than 30^{O}C
Dose	• 800mg (4 x 200mg capsules) orally 12-hourly for 5 days • No dose adjustment is required for renal or hepatic impairment or the elderly (see precautions above) • 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
	• 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.
	• Preparation of the solution:
	  ○ Open FOUR (4) capsules and transfer contents into an oral syringe. Discard empty capsule shells
	  ○ Add approximately 40 mL of water to the oral syringe
	  ○ Mix/stir the capsule contents and water for 3 minutes.
	  1. Insoluble capsule contents may not dissolve completely.
	  2. Reconstituted solutions prepared according to directions may have visible undissolved particulates and are acceptable for oral administration.
	  ○ Administration should occur as soon as possible after the preparation and no later than 2 hours after the preparation.
	• For administration via enteral tube:
	  ○ Prior to administration redisperse the suspension by mixing or stirring the oral syringe for 1 minute prior to administration
	  ○ Flush enteral tube with 5 mL of water prior to administration.
	  ○ Administer entire volume from the administration syringe.
	  ○ 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 • 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 • 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	• It may be difficult to distinguish between adverse effects of molnupiravir and the signs and symptoms of COVID-19.
	• 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:
	  ○ Common (>1%): diarrhoea, nausea, dizziness, headache
	  ○ Uncommon (0.1-1%): rash, urticaria
	• 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

Sotrovimab [1,2,3,4,6,7,9,10,13,23] **ID Approval and patient consent required (verbal or written)** **For the most recent updates on the use of Sotrovimab in patients with COVID-19 visit the Sotrovimab drug guideline available via the NSW Clinical Excellence Commission**	
Drug Class	• Recombinant human IgG1 monoclonal antibody targeting the spike protein of SARS-CoV-2, which is thought to prevent membrane fusion after the virus binds to the human ACE2 receptor.
Indications	Prescribe on advice of Infectious Diseases only. • Current advice from the National COVID-19 Clinical Evidence Taskforce is states "Where infection with Omicron BA.2 is confirmed or considered likely, use of sotrovimab should only be considered where other treatments are not suitable or available"
Contra-indications	• Hypersensitivity to sotrovimab, or any of the excipients in the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies. • Exercise caution in patients with a history of anaphylaxis to other medicines. • Children less than 12 years old or weighing < 40kg • For a full list of precautions and considerations for special populations please visit the sotrovimab drug guideline available via the NSW Therapeutic Advisory Group
Precautions	• Renal Impairment: No dose adjustment required • Hepatic Impairment: No dose adjustment required • Pregnancy: No data on the use of sotrovimab in pregnant patients. ○ Use should be considered in pregnant patients, particularly for patients in their second and third trimesters of pregnancy, with additional risk factors for severe COVID-19 infection.

	• Breastfeeding: Sotrovimab may be used during breastfeeding. The benefits of breastfeeding for both mother and infant are well established. These should be carefully considered against the current unknown but unlikely risks for the use of sotrovimab during breastfeeding. For detailed information, refer to the SA Health Medicines Information sheet "Sotrovimab and Breastfeeding" (also accessed via salus.sa.gov.au)
Drug Interactions	• No formal interaction studies have been conducted with sotrovimab. Sotrovimab is not renally excreted or metabolised by the CYP450 enzymes • For up to date information regarding drug interactions with sotrovimab please check the University of Liverpool COVID-19 resource page • Interaction with COVID-19 vaccination has not been determined. The US Centers for Disease Control and Prevention advises delaying COVID-19 vaccination until 90 days after administration of monoclonal antibodies as part of COVID-19 treatment, to avoid potential interference with the immune response to the COVID-19 vaccination. This advice applies to those who have not received any vaccine dose as well as those who have received the first dose but not the second dose.
Preparation and storage	• Available as a single use vial of 500 mg in 8 mL (62.5 mg/mL) concentrated injection solution for infusion (after diluting). The solution in the vial should be clear and colourless to yellow or brown. • Store refrigerated at 2 - 8^{o}C in original package. Protect from light. Do not freeze.
Dose	• 500mg as a single dose intravenous infusion over 30 minutes
Administration	1. Remove one vial containing 500mg in 8 mL sotrovimab solution from refrigerator at least 15 minutes before preparation of the infusion. 2. Visually inspect vial to ensure no particulate matter is present and there is no damage to the vial (discard if present). 3. Gently swirl the vial several times without creating air bubbles before using - (do NOT shake vigorously). 4. Withdraw 8 mL solution from the sotrovimab vial and inject into a 50 mL or 100mL bag of 0.9% sodium chloride or 5% glucose. 5. Prior to infusion, to mix, gently rock the infusion bag back and forth 3 to 5 times. Do NOT invert the bag. Avoid forming air bubbles. 6. Do not use the same IV line to administer other medications at the same time. 7. Attach an infusion set to the infusion bag using standard bore tubing. Information from the manufacturer states the additional use of a 0.2 micrometre in-line filter is recommended but not essential. 8. Prime the infusion set with sotrovimab infusion and then infuse intravenously over 15 minutes (if using 50 mL bag) or 30 minutes (if using 100 mL bag) (until the bag is empty) via a central or peripheral line. 9. After the sotrovimab infusion is completed, flush the giving set with at least 20 mL of 0.9% sodium chloride or 5% glucose (at the same rate as the sotrovimab infusion).
Monitoring	• Observe the patient for 30 minutes after the infusion is completed in case of infusion reaction or anaphylaxis
Infusion reactions	• Infusion reactions include fever, chills, dizziness, dyspnoea, pruritis and rash. • For mild to moderate infusion reactions, slow or stop the infusion and treat accordingly • Anaphylactic reactions are rare but are a medical emergency. Stop the infusion and commence treatment immediately (see CALHN Anaphylaxis: Management Guidelines CALHN OWI-04038)
Adverse Effects	• It may be difficult to distinguish between adverse effects of sotrovimab and signs and symptoms of COVID-19.

	• As a new medication, adverse reactions to sotrovimab continue to be investigated. Refer to the product information for a complete list of possible adverse effects. To date reactions include: ▪ Common (>1%): diarrhoea (1%), hypersensitivity reactions (includes rash (2%), infusion-related reaction, bronchospasm). ▪ Rare: anaphylaxis. • 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 sotrovimab patient information leaflets can be found here • Sotrovimab patient information leaflets are available via the NSW Clinical Excellence Commission

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-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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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.
	• Characteristics:
	  ○ no symptoms; or
	  ○ mild upper respiratory tract symptoms; or
	  ○ cough, new myalgia or asthenia without new shortness of breath or a reduction in oxygen saturation
	  ○ 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.
	• Characteristics:
	  ○ fatigue, fever > 38ºC or persistent cough
	  ○ clinical or radiological signs of lung involvement
	  ○ 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: • respiratory rate ≥ 30 breaths/min • oxygen saturation ≤ 92% at a rest state on ≥ 4L/min oxygen via nasal prongs • arterial partial pressure of oxygen (PaO_2) / inspired oxygen fraction (FiO_2) ≤ 300

Critical illness (ICU)	Adult patients meeting any of the following criteria:
	• Respiratory failure as defined by:
	  ○ severe respiratory failure (PaO_2/FiO_2 < 200), respiratory distress or acute respiratory distress syndrome
	  ○ deterioration despite advanced forms of respiratory support (non-invasive ventilation, high flow nasal oxygen) OR requiring mechanical ventilation
	OR
	• Other signs of significant deterioration:
	  ○ hypotension or shock
	  ○ impairment of consciousness
	  ○ other organ failure

End of Appendix 1