SA Health

COVID-19:
Treatment recommendations for hospitalised adult patients

Statewide Clinical Guideline - Adoption of CALHN Guideline

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Version 5.0

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Government of South Australia | Health
Central Adelaide Local Health Network

GUIDELINE

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Title	COVID-19: Treatment recommendations for hospitalised adult patients			
Scope	All CALHN clinical staff in acute care hospitals			
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			
Risk rating	☐ Extreme	☐ High	☒ Medium	☐ Low
Monitoring/audit	☒ Scheduled for audit		☐ Not scheduled for audit	
Title and reference of parent SA Health Policy	N/A			
Summary (three sentences maximum)	This guideline provides recommendations on the antiviral and immunomodulatory medications available for patients hospitalised with COVID-19 in CALHN.			
Keywords (five to eight)	COVID-19, Baricitinib, Molnupiravir, Nirmatrelvir, Ritonavir, Remdesivir, Tocilizumab, Sarilumab, Dexamethasone, Sotrovimab.			

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 update. 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.	February 2026
4.6	Non-scheduled review. Nirmatrelvir/ritonavir no longer contraindicated but still to be generally avoided in patients with eGFR<30ml/min and can be used in patients on haemodialysis provided prescribing is done in conjunction with the renal team. ATSI patients aged >30 years of age now only require 1 risk factor for treatment eligibility for mild disease. Addition of “can be ceased after 3 days if patient well enough to discharge” to remdesivir use in moderate illness. Changes to broken links in document.	December 2025

GUIDELINE

COVID-19: Treatment recommendations for hospitalised adult patients

Introduction

- Since the emergence of COVID-19 there have been significant developments in the antiviral and immunomodulatory medications recommended for patients hospitalised with COVID-19.
- This guideline only addresses the use of disease-modifying treatments for COVID-19 in hospitalised adult patients.
- 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 information regarding the prevention or chemoprophylaxis for the prevention of COVID-19.
- For information related to the management and care of patients with COVID-19 please refer to:
  - 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

Topics covered in this guideline

For detailed information on the following topics click on the links below:

1. Definition of COVID-19 disease severity for adults
2. Risk factors for progressing to severe or critical illness
3. Classification of immunosuppressed patients including medications associated with a reduced immune response to COVID-19 vaccination
4. COVID-19 treatment recommendations for hospitalised adults according to disease severity (excluding pregnancy/breastfeeding) – mild illness
5. COVID-19 treatment recommendations for hospitalised adults according to disease severity (excluding pregnancy/breastfeeding) – moderate to critical illness
6. Assessing a patient for nirmatrelvir plus ritonavir (Paxlovid®)
7. COVID-19 treatment recommendations for hospitalised pregnant and breastfeeding adults
8. Access and restrictions to therapy
9. Treatments for COVID-19 - Drug Monographs

Sotrovimab
Remdesivir
Nirmatrelvir plus ritonavir
Baricitinib
Sarilumab
Dexamethasone
Molnupiravir
Tocilizumab

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

2. Risk factors for progressing to severe or critical illness[1,28,29]

- 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
- 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

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.

* 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.

3. Classification of Immunosuppressed Patients

Immunosuppressed 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.

NOTE asplenic or hyposplenic patients are not classified as immunosuppressed

Medications associated with a reduced immune response to COVID-19 vaccination

Clinicians may use their judgement for medications which are not listed

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.
Cell transplant recipients	• 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** ○ 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 pre-malignant haematological disorder (e.g. aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic therapy within the last 12 months
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 • obinutuzumab, 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 (PBS eligible within 3 months)* Sphingosine 1-phosphate receptor modulators • fingolimod, siponimod (PBS eligible within 3 months)* 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)* • leflunomide, cladribine Other agents • PBS eligible with treatment within 3 months: abatacept • Not included in PBS eligible medications*: belimumab, blinatumomab, dimethyl fumarate, venetoclax, daratumumab
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
Multiple immunosuppressants or combination immunosuppression	Combination therapy where the cumulative effect is severely immunosuppressive*
	• 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 severe intellectual or physical disabilities requiring residential care • Down Syndrome • Cerebral Palsy • Congenital heart disease • Thalassemia • Sickle cell disease • Other haemoglobinopathies not already listed

* 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) refer patient for treatment via SA Health referral webpage

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)

Health

Title	COVID-19: Disease-modifying treatment recommendations for hospitalised adult patients

4. COVID-19 treatment recommendations for hospitalised adult patients (excluding pregnancy/breastfeeding- see page 10)

See page 11 for information on prescribing restrictions and access to therapies in CALHN

Mild illness not requiring oxygen

For all hospitalised patients consider VTE prophylaxis and empiric influenza treatment* until results of respiratory viral panel available

- **Immunosuppressed** patients (all ages) irrespective of vaccination status
- **Previous COVID-19 infection requiring hospitalisation** (all ages) irrespective of vaccination status or risk factors
- **Aged ≥ 70 years** irrespective of vaccination status or risk factors
- **Aged 50 to 69 years** irrespective of vaccination status **PLUS** ≥ 1 risk factor (Box 1)
- **Aboriginal or Torres Strait Islander AND Aged ≥ 30 years** irrespective of vaccination status **PLUS** ≥ 1 risk factor (Box 1)
- **Aged < 50 years or < 30 years if Aboriginal or Torres Strait Islander** irrespective of vaccination status **PLUS** ≥ 3 risk factors (Box 1)

First Line:
If symptom onset **≤ 5 days AND NO** contraindications or drug interactions
Nirmatrelvir plus ritonavir

Second Line:
Symptom onset **≤ 7 days AND** contraindications to nirmatrelvir plus ritonavir
Remdesivir

Third Line:
Symptom onset **≤ 5 days AND** nirmatrelvir plus ritonavir and remdesivir contraindicated or unavailable
Molnupiravir (see Box 3)

- **Aged < 50 years** (or < 30 years if Aboriginal or Torres Strait Islander) **PLUS** 1 or 2 risk factors (Box 1)

First Line:
If symptom onset **≤ 5 days AND NO** contraindications/ drug interactions
Nirmatrelvir plus ritonavir

See Box 3 for patients contraindicated from taking nirmatrelvir plus ritonavir

NOTE: Supportive care recommended for patients who are at **low risk of progressing to severe illness** (i.e. not up to date vaccination status) 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 3: 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 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 (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

Box 2: Dosing Recommendations

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
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).
***Oseltamivir:** **CrCl >30mL/min:** 75mg orally twice daily, **CrCl 10-30mL/min**: 75mg orally once daily, **CrCl <10mL/min**: 75mg orally alternate daily for 5 days **IF** Influenza confirmed. Cease immediately if viral panel negative for influenza

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Reference	CALHN-GDE05778	Version	3.0	Approved	2022

5. COVID-19 treatment recommendations for hospitalised adult patients (excluding pregnancy/breastfeeding- see page 10)

See page 11 for information on prescribing restrictions and access to therapies in CALHN

Moderate illness on supplemental oxygen	Severe illness on high flow oxygen	Critical illness on non-invasive or mechanical ventilation
For all hospitalised patients: VTE prophylaxis^ AND for all patients with moderate to critical illness: Dexamethasone Consider empiric influenza treatment* until results of respiratory viral panel available		
remdesivir **PLUS** if no improvement or increasing oxygen requirement **ADD** **baricitinib** (if baricitinib contraindicated contact ID)	remdesivir **PLUS** baricitinib **OR** If clinical signs of deterioration# and not already on baricitinib remdesivir* **PLUS** tocilizumab	**Non-invasive ventilation / high flow oxygen/mechanical ventilation** and not already on baricitinib tocilizumab (can continue remdesivir* if already commenced)
	# rapidly increasing oxygen requirement despite high flow oxygen (≥ 4L/min), respiratory distress or signs of acute respiratory distress syndrome, sepsis or other organ failure	

Box 1: Dosing Recommendations

Baricitinib: Daily oral dose for up to 14 days. Modify dose according to renal function**: eGFR > 60mL/min** 4mg daily, **eGFR 30-60mL/min** 2mg daily, **eGFR 15-30mL/min** 2mg every second day. **eGFR < 15mL/min:** not recommended

Dexamethasone: 6mg oral or IV for up to 10 days (can be ceased at discharge if this is before 10 days). Seek specialist advice if on long term or high dose corticosteroids prior to admission

Remdesivir: Do not start remdesivir if > 10 days since symptom onset OR in patients on mechanical ventilation but it may be continued if commenced prior to ventilation. Dose: 200mg IV load on day 1 then 100mg IV daily for another 4 days (total 5-day course but can be ceased after 3 days if patient well enough to discharge). **If eGFR < 30mL/min and/or on dialysis–** discuss with clinical pharmacy, Infectious Diseases or Renal (see drug monograph).

Tocilizumab (ID approval required outside of ICU): IV single dose based on weight. If ≤ 40kg: **8mg/kg**, > 40kg and ≤ 65kg: **400mg**, > 66kg and ≤ 90kg: **600mg**, > 90kg: **800mg**

VTE Prophylaxis^: Recommended for all hospitalised patients with COVID-19 unless contraindicated (i.e. major bleeding). **CrCl > 30mL/min**: enoxaparin 40mg subcutaneous injection daily. **CrCl < 30mL/min**: enoxaparin 20mg subcutaneous injection daily

Note: Patients in ICU requiring initiation of these medications after hours (between 10pm and 8am) do NOT require ID approval however they should be discussed the next day during the ICU/ID COVID ward round

***Oseltamivir: CrCl >30mL/min:** 75mg orally twice daily, **CrCl 10-30mL/min**: 75mg orally once daily, **CrCl <10mL/min**: 75mg orally alternate daily for 5 days **IF** Influenza confirmed. Cease immediately if viral panel negative for influenza

6. Assessing a patient for nirmatrelvir plus ritonavir (Paxlovid®) – 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)
- Unable to swallow tablets
- Cognitively impaired or unable to manage medications
- 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 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

Give nirmatrelvir plus ritonavir (Paxlovid)

Yes

Nirmatrelvir plus ritonavir (Paxlovid) dosing

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: not recommended, see drug monograph for patients on dialysis

Health
Central Adelaide

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7. COVID-19 treatment recommendations for hospitalised pregnant and breastfeeding adult patients

(refer to Box 3 for dosing recommendations)

See page 11 for information on prescribing restrictions and access to therapies in CALHN

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 2) taking into account the harm benefit ratio for both mother and fetus. Seek advice from ID.

Mild illness not requiring oxygen	**Moderate illness** on supplemental oxygen	**Severe illness** high flow oxygen	**Critical illness** non-invasive ventilation or mechanical ventilation

VTE Prophylaxis (recommended for all hospitalised patients with COVID-19 unless contraindication e.g. major bleeding)
Consider empiric influenza treatment* until results of respiratory viral panel available

immunosuppressed (regardless of vaccination status)
OR
unvaccinated or vaccination status not up to date (Box 1) with one or more risk factor(s) for progressing to severe illness (Box 2)
All patients must be ≤ 7 days since symptom onset
1st trimester: **Contact ID**
2nd or 3rd trimester or breastfeeding: **remdesivir***
(discuss with ID if patient is ineligible/declines remdesivir therapy)

For all patients with moderate to critical illness consider corticosteroid e.g. dexamethasone (obtain guidance from obstetric medicine for preferred corticosteroid in pregnancy; prednisolone or hydrocortisone may be preferred first – for appropriate dose conversion see here. Seek specialist advice for patients taking long term or high dose corticosteroids prior to admission)

remdesivir *
PLUS
If no improvement (e.g. evidence of systemic inflammation) or increasing oxygen requirement
tocilizumab

remdesivir*
PLUS
tocilizumab

tocilizumab
Continue **remdesivir*** if it has already been commenced prior to ventilation

Box 1: 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. Refer to ATAGI for more information on booster doses and definition of up to date vaccine status.

Box 2: Risk factors for progressing to severe illness (see page 4 for more detail): Immunosuppressed, diabetes/gestational diabetes, obesity (BMI >40kg/m^2), renal impairment , coronary artery disease, cardiomyopathies or heart failure, respiratory compromise, chronic liver disease (cirrhosis), disability with multiple comorbidities and/or frailty , 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 neurological diseases including: dementia, stroke, demyelinating conditions (i.e. multiple sclerosis), past COVID-19 infection episode resulting in hospitalisation

Box 3: Dosing Recommendations
Dexamethasone: 6mg oral or IV for up to 10 days (can be ceased at discharge if this is before 10 days).
Remdesivir* (mild illness): 200mg IV on day 1 then 100mg on day 2 and 3. 3 day course only). **If eGFR < 30mL/min and/or on dialysis–** discuss with clinical pharmacy
Remdesivir* (moderate to critical illness): 200mg IV load on day 1 then 100mg IV daily for another 4 days (total 5 day course but can be ceased after 3 days if patient well enough to be discharged). **If eGFR < 30mL/min and/or on dialysis–** discuss with clinical pharmacy, Infectious Diseases or Renal (see drug monograph). There is a paucity of evidence of efficacy for remdesivir in COVID-19 infection. Consider using remdesivir for selected pregnant or breastfeeding patients hospitalised with moderate to severe COVID-19 illness who do not require ventilation, with ID guidance. Pregnant patients were excluded from all clinical trials of remdesivir in COVID-19.
Tocilizumab: IV single dose based on weight at the time of clinical need. If ≤ 40kg: 8mg/kg, > 40kg and ≤ 65kg: 400mg, > 66kg and ≤ 90kg: 600mg, > 90kg 800mg
VTE Prophylaxis: Enoxaparin 40mg subcut injection daily if CrCl > 30mL/min or enoxaparin 20mg subcut injection daily if CrCl < 30mL/min. 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
***Oseltamivir:** **CrCl >30mL/min:** 75mg orally twice daily, **CrCl 10-30mL/min**: 75mg orally once daily, **CrCl <10mL/min**: 75mg orally alternate daily for 5 days **IF** Influenza confirmed. Cease immediately if viral panel negative for influenza

NOTE 2: Given the limited data in pregnant and breastfeeding patients, **baricitinib** should only be used in clinical trials. Molnupiravir and nirmatrelvir plus ritonavir are not recommended in pregnant or breastfeeding women.
NOTE: If corticosteroids are required for fetal lung maturity in women at risk of preterm birth obtain guidance from obstetric medicine regarding the appropriate steroid and dose to be prescribed.

8. Access and restrictions

Disease-modifying therapy ^	ID Approval required *	Online declaration form	Available on PBS for COVID-19	Registered in Australia for COVID-19	Verbal Consent required@	After hours access Available¥
Baricitinib	No*	Yes	No	No – off label use	Yes	Yes
Dexamethasone	No	No	No	No – off label use	Yes	Yesβ
Molnupiravir	No*	Yes	Yes	Provisionally	Yes	No
Nirmatrelvir plus ritonavir	No*	Yes	Yes	Provisionally	Yes	No
Remdesivir#	No*	Yes	No	Provisionally	Yes	Yes
Sotrovimab	Yes	No	No	Provisionally	Yes	No
Tocilizumab*	Yes	No	No	Provisionally	Yes	4G178 (fridge)

^ The SA Formulary Committee has approved the provisional formulary listing of the medications above for indications listed in the National Covid-19 Clinical Taskforce Guidelines.

@ Informed consent should be obtained for the use of medicines to treat COVID-19, especially those that are unregistered or used in an off-label manner. The consent should be documented in the patient's Health Record, including when verbal informed consent is obtained. More information regarding where consent is recommended or required can be found here.

¥ After hours availability may change according to usage, patient numbers and stock availability. Molnupiravir and nirmatrelvir plus ritonavir are not available after hours (unless the patient is day 5 of symptoms, it can be dispensed the next day). If stock not available in machines mentioned above after searching "global find" in ADC then please contact on-call pharmacist on pager 22161

β Both the oral and IV formulations are available in many ADC machines throughout the hospital including but not limited to: 4G148, 4G78, 6G211 and 6G206

* ID approval not required for baricitinib, remdesivir, molnupiravir, nirmatrelvir plus ritonavir if prescribed in line with recommendations within these guidelines. Tocilizumab requires ID approval except when given overnight in ICU.

Sotrovimab, molnupiravir, nirmatrelvir plus ritonavir and remdesivir are all accessed via the National Medical Stockpile (NMS). There are specific criteria for access to these medications (see individual drug monographs for indications per the stockpile and contra-indications/exclusions)

During business hours (7 days per week 8:45am-5pm)

- Place a medication requisition order through Sunrise and mark as urgent
- Contact in-patient pharmacy (ext. 44988) to arrange stock delivery/collection

9. Treatments for COVID-19 – Drug Monographs

Nirmatrelvir plus Ritonavir (Paxlovid®) [1,7,15,16, 35 , 35, 37]

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.
	• **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	• **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. • Exercise caution in patients with a history of anaphylaxis to other medicines. • **Hepatotoxicity** - Caution should be exercised in patients with pre-existing liver disease, or hepatitis. Hepatic transaminase elevations, clinical hepatitis and jaundice have been reported in patients using ritonavir. • **Risk of HIV-1 Resistance Development** - Due to the co-administration of low dose ritonavir, there may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.
Storage and presentation	• 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, see precautions • **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	• Swallow the tablets whole with or without food. • Do not chew, break or crush the tablets. • The daily blister for Paxlovid® contains two separated parts each containing 2 tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the

	standard dose. Therefore, patients with moderate renal impairment should be alerted on the fact that only one tablet of nirmatrelvir with the tablet of ritonavir should be taken every 12 hours.
Monitoring	• 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.

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

Patient consent (verbal or written) required

Stock not available after hours in CALHN

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 with symptom onset of no more than 5 days and who do not require supplemental oxygen and are: ○ 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 to 69 years 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** ≥ 3 risk factors) for progressing to severe or critical illness (irrespective of vaccination status) • 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.
	  ▪ Insoluble capsule contents may not dissolve completely.
	  ▪ 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

Remdesivir[1,2,5,7,8,10,11,12,25]

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	○ **Treatment of mild COVID-19 Illness:** • 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 illness **OR** ▪ Aged ≥ 70 years irrespective of vaccination or risk factors for progressing to severe illness **OR** ▪ Aged < 50 years or < 30 if Aboriginal and/or Torres Strait Islander **with THREE** or more risk factors for progressing to severe 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. ○ **Treatment of moderate to critical illness:** ○ Remdesivir may be considered for patients with a confirmed diagnosis of COVID-19 or known contact of a confirmed case with syndrome consistent with COVID-19 awaiting confirmation by diagnostic testing; **AND** ○ Aged ≥ 18 years, or aged 12 to 17 years and weighing > 40 kg; **AND** ○ With oxygen saturation ≤ 92% on room air and requiring supplemental oxygen; **AND** ○ ≤ 10 days since symptom onset ○ For use in moderate disease vaccination status of the patient does NOT matter • Remdesivir is **NOT** indicated for patients requiring invasive mechanical ventilation or ECMO, although it may be continued if it was started prior to ventilation commencing. • Unless corticosteroids are contraindicated (see dexamethasone monograph above), remdesivir should be given in conjunction with dexamethasone for patients requiring supplemental oxygen (i.e. patients being treated for moderate to critical COVID-19)

	• Remdesivir is available via the National Medical Stockpile and availability is expected to fluctuate with demand and constraints in the supply chain. In the context of shortages remdesivir should be reserved for those patients who will likely benefit the most including: ▪ ≤ 7 days since symptom onset ▪ Not requiring high flow nasal oxygen ▪ Life expectancy greater than ONE year
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 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

[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

	▪ 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). Can be ceased after 3 days of therapy if patients are well enough to be discharged i.e. no longer requiring supplemental oxygen.
Administration	• There are different formulations of remdesivir available via the National Medicines Stockpile and administration instructions may vary. • 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 daily creatinine, electrolytes, urea, LFTs and complete blood exam ▪ 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	• CALNH Remdesivir Consumer Information leaflets can be found here • Remdesivir patient information leaflets are also available via the NSW Clinical Excellence Commission

Dexamethasone[1,2,5,7,9,11] **For more detailed information on the use of dexamethasone in patients with COVID-19 visit the COVID-19 National Clinical Evidence Taskforce Guidelines**	
Drug Class	○ Corticosteroid
Indications	○ Dexamethasone is recommended for all adult patients with confirmed COVID-19 infection AND are receiving oxygen (including mechanically ventilated patients) ○ Do not routinely use in patients with COVID-19 who do not require oxygen
Contra-indications	• Hypersensitivity to dexamethasone or any excipients of the tablet or injection or to other corticosteroids • Concomitant administration of live virus vaccines (risk of severe systemic infection)
Precautions	• Seek specialist advice for patients taking long term or high dose corticosteroids prior to admission • Patients with primary or secondary adrenal insufficiency, rheumatologic and other chronic conditions treated with corticosteroids may not be able to mount a normal stress response in the event of COVID-19 infection. Administration of physiologic stress doses of corticosteroids may need to be considered to avoid potentially fatal adrenal failure • Pregnancy: corticosteroid treatment is recommended for the treatment of moderate/severe or critical COVID-19 infections. Choice of steroid should be guided by Obstetric Medicine, Infectious Diseases and ICU (if required) at the time of treatment. Patients may be offered dexamethasone or prednisolone depending on their gestation, pregnancy details, comorbidities and other illness factors. • Given the short duration of treatment for COVID-19 many of the recognised precautions for the use of corticosteroids may not apply. • The treating doctor should assess if treatment with dexamethasone puts the patient at substantial risk of harm due to concurrent (non COVID-19) infection. This assessment must not delay treatment with dexamethasone • For a full list of precautions and considerations for special populations such as pregnancy and breastfeeding please visit the dexamethasone drug guideline available via the NSW Therapeutic Advisory Group.
Drug Interactions	• Dexamethasone is a moderate inducer of CYP3A4 and P-glycoprotein (P-gp) and a substrate for CYP3A4. Use with CYP3A4 inhibitors may increase dexamethasone concentrations, while use with CYP3A4 inducers may decrease dexamethasone concentrations and efficacy. • The effects of anticoagulant agents are usually decreased (but may be increased in some patients) with concurrent corticosteroid treatment. Close monitoring of the INR or prothrombin time is recommended.

	• Concomitant use of drugs that irritate the gastrointestinal lining with dexamethasone may increase the risk of peptic ulceration and bleeding • For more detailed information regarding drug interactions with dexamethasone check the University of Liverpool COVID-19 resource page
Preparation	• Intravenous formulations: 4mg/mL or 8mg/2mL • Oral formulation: 4mg and 0.5mg tablets

Dose and administration	• 6mg via intravenous injection or 6mg orally with food ONCE daily for up to 10 days*
	  • If giving via intravenous injection give as a slow injection over 3-5 minutes
	  • May be diluted with 10 mL of sodium chloride 0.9% to facilitate slow injection
	* If well enough to discharge prior to the 10 day course being completed dexamethasone can be ceased on discharge

Adverse Effects	• Given the short duration for COVID-19 of treatment many known corticosteroid adverse effects are unlikely to occur
	• Some common adverse effects that may occur with short term use of dexamethasone include:
	  • Transient itching, burning or tingling in perineal area (after high dose rapid IV bolus)
	  • Infection
	  • Electrolyte and fluid disturbances including: hypernatraemia, hypervolaemia, hypokalaemia
	  • Hypertension,
	  • Hyperglycaemia,
	  • GI disturbances including increased appetite and dyspepsia
	  • Delayed wound healing and bruising
	  • Facial flushing
	  • Myopathy, muscle weakness
	  • Psychiatric effects (euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis are less common).

Monitoring	• Clinicians should monitor for potential adverse effects listed above including monitoring blood sugar levels (especially if known diabetic) and creatinine and electrolytes • Baseline testing for hepatitis B, HIV, HCV should be undertaken for all patients and consider strongyloides and tuberculosis testing according to epidemiological risk factors. Dexamethasone treatment should **NOT** be delayed pending results of baseline tests
Patient information	• Dexamethasone product information and consumer medicines information leaflets are available via MIMS

Baricitinib[1,2,3,7,8,11,13,14,15] **ID approval and patient consent (verbal or written) required** **For more detailed information on the use of baricitinib in patients with COVID-19 visit the Clinical Excellence Commission baricitinib guideline**	
Drug Class	• Janus Kinase (JAK) 1 and 2 inhibitor, disease-modifying anti-rheumatic drug (DMARD), immunomodulator
Indications	• Off-label use of baricitinib may be considered for patients with a current diagnosis of COVID-19:

	▪ Who require supplemental oxygen, high-flow oxygen and/or non-invasive ventilation including those who may be intolerant of steroid therapy • Baricitinib is not first line for patients on mechanical ventilation but can be continued if a patient progresses from needing high-flow oxygen/non-invasive ventilation to mechanical ventilation • Baricitinib should **NOT** be given to patients who have already received sarilumab or tocilizumab • Unless corticosteroids are contraindicated (see dexamethasone monograph above), baricitinib should be given in conjunction with dexamethasone
Contraindications	• Hypersensitivity: contraindicated in patients with known hypersensitivity to baricitinib or any of the excipients in the product. • Pregnancy and breastfeeding • Renal impairment [2]: Not recommended for patients on dialysis or patients with acute kidney injury or eGFR < 15mL/min/1.73m^2. • Patients with serious active infections (other than COVID-19) • Live vaccines should not be given concomitantly
Precautions	• Thrombosis: Baricitinib may increase the risk of venous thromboembolism (VTE). Use with caution in individuals with an increased risk of thrombosis. • Use with caution if haemoglobin < 80 g/L, lymphocyte count < 0.2 x 10^9/L or neutrophil count < 0.5 x 10^9/L • Renal impairment: Dose reduction required in patients with eGFR 30-60 mL/min/1.73m^2 • Hepatic: Baricitinib has not been studied in patients with severe hepatic impairment. It should only be used in patients with severe hepatic impairment if the potential benefit outweighs the potential risk of harm • Gastrointestinal (GI): GI perforations have been reported. Use with caution in patients at risk of GI perforation. Evaluate new onset abdominal symptoms • Infection: use is associated with an increased risk of serious infection including bacterial, viral, fungal and opportunistic infection, additive risk when used in combination with other immunosuppressive therapy. Patients should be monitored for signs and symptoms of infection. Patients should be evaluated for latent tuberculosis infection.
Drug Interactions	• Strong OAT3 inhibitors such as gemfibrozil and probenecid may increase concentrations of baricitinib – see below for dose adjustments • Additive immunosuppressive risk when used with other immunomodulatory agents e.g. methotrexate, corticosteroids (excluding dexamethasone given for COVID-19), tocilizumab, adalimumab, rituximab and anakinra. Use of monoclonal antibodies targeting cytokines (e.g. TNF-alpha, interleukin-1, interleukin-6) or T-cells within the last 4 weeks and monoclonal antibodies targeting B-cells within the last 3 months are contraindicated. • Clozapine: increased risk of agranulocytosis • Live vaccines should be avoided just prior to and during treatment with baricitinib. Specialist input should be obtained regarding timing of future vaccinations

[2] 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 a full list of drug interactions check the University of Liverpool COVID-19 resource page
Presentation and storage	• Available as: ○ 2 mg film-coated tablets ○ 4 mg film-coated tablets • Store below 30^{O}C in original package
Dose	• 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 • Oral daily dose for up to 14 days or until discharge – whichever comes first • 4mg orally daily if eGFR > 60mL/min/1.73m^2 • 2mg orally daily if eGFR 30-60mL/min/1.73m^2 • 2mg orally every second day if eGFR 15-29mL/min/1.73m^2 • Do NOT use if eGFR < 15mL/min/1.73m^2 • Patients taking strong OAT3 inhibitors, such as probenecid or gemfibrozil, prescribe half the dose which would be given for patient's renal function
Administration	• Can be given with or without regard to food • Do not crush or break the tablet • For patients who are unable to swallow whole tablets, place tablet(s) to achieve desired dose in a closed oral syringe with room temperature water and disperse by gentle swirling until an even suspension is formed. Tablet may take 5 minutes to completely disperse. • Dispersed tablets are stable in water for up to 4 hours; however, the solution should be administered immediately whenever possible. The container should be rinsed with additional room temperature water and these contents also administered. **Dispersion instructions for 2mg and 4mg baricitinib tablets** **Administration via** / **Dispersion volume of water** / **Container rinse volume** Oral dispersion / 5-10 mL / At least 5 mL Gastrostomy tube / 15 mL / At least 15 mL Nasogastric tube* / 30 mL / At least 15 mL * To avoid clogging of small diameter tubes (smaller than 12 Fr), the syringe can be held horizontally and shaken several times • See special instructions in NSW Therapeutic Advisory Group baricitinib drug guideline for further information
Handling	• Intact baricitinib tablets can be handled with standard precautions for handling of oral medications • 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	• As baricitinib is a new medication, patients should have appropriate clinical and laboratory monitoring including:

	• Baseline and daily creatinine, electrolytes and urea as well as LFTs and complete blood exam.
	• Interrupt treatment if:
	  • Neutrophil count < 0.5 x 10^9 cells/L
	  • Lymphocyte count < 0.2 x 10^9 cells/L
	  • Haemoglobin < 80g/L
	  • Increases in ALT or AST are observed and drug-induced liver injury is suspected
	• Baseline testing for hepatitis B, HIV, HCV should be undertaken for all patients and consider strongyloides and tuberculosis testing according to epidemiological risk factors. Baricitinib treatment should **NOT** be delayed pending results of baseline tests

Adverse Effects	• As the use of baritinib for COVID-19 is off-label, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use • Common (>1%): infections (including serious and opportunistic), hypercholesterolaemia, thrombocytosis (not associated with thrombotic events), nausea (especially in first 2 weeks), abdominal pain, headache, increased creatine kinase • Infrequent (0.1–1%): thrombosis, neutropenia, lymphopenia, anaemia, acne, vomiting, hypertriglyceridaemia, increased liver enzymes • 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	• Baricitinib patient information leaflets are available via the NSW Therapeutic Advisory Group • Example patient consent forms can be found here

Sarilumab[1,2,3,7,8,11,16,17,18] **ID approval and patient consent (verbal or written) required** **For more detailed information on the use of sarilumab in patients with COVID-19 visit the Clinical Excellence Commission sarilumab guideline**	
Drug Class	• Anti-rheumatic, cytokine modulator, interleukin-6 (IL-6) receptor antagonist/inhibitor monoclonal antibody (human).

Indications	• Off-label use of sarilumab may be considered for non-pregnant/non-breastfeeding adults with a current diagnosis of COVID-19:
	  ▪ who require supplemental high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation, particularly where there is evidence of systemic inflammation such as:
	  ○ Elevated C-reactive protein (CRP), D-dimer, lactate dehydrogenase and ferritin
	  AND
	  ▪ when baricitinib is contraindicated or not recommended (i.e. mechanical ventilation)
	• If available & not contraindicated, sarilumab is the preferred IL-6 inhibitor during tocilizumab shortage

	• It is recommended to commence sarilumab within 24 hours of commencing supplemental high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation • Unless corticosteroids are contraindicated (see dexamethasone monograph above), sarilumab should be given in conjunction with dexamethasone
Contraindications	• Hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies. • Sepsis or active, severe infections from non-COVID-19 pathogens • Live and live-attenuated vaccines should not be given concurrently
Precautions	• Hepatic impairment: Exercise caution in patients with active hepatic disease or impairment, including abnormal liver enzymes (ALT or AST greater than 1.5 times the upper limit of normal (ULN)) • Use with caution and monitor closely if neutrophil count < 2 x 10^9/L or platelets < 150 x 10^9/L • Renal impairment: No dose adjustment required • Gastrointestinal (GI): Use with caution in patients at risk of GI perforation. Monitor for new onset abdominal symptoms • A history of anaphylaxis to other medicines • A history of recurring or chronic infection, or with underlying conditions (e.g. diabetes) which may predispose patients to infections. • A history of HIV, positive core antibody for hepatitis B, prior HCV infection or symptomatic EBV infection • A history of tuberculosis/tuberculosis exposure • Concurrent immunosuppressive/anti-rejection therapy increases the risk of infection and should be avoided. • Pregnancy and breastfeeding: sarilumab is not recommended for use in the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval • Use in children or adolescents < 16 years of age
Drug Interactions	• Concurrent use of immunosuppressive/anti-rejection therapy (e.g. infliximab) increases the risk of infection and should be avoided • Clozapine: increased risk of agranulocytosis / haematological toxicity • The therapeutic effect of recent vaccinations e.g. COVID-19 vaccination may be diminished. Specialist input should be obtained regarding timing of future vaccinations. Concurrent use of live vaccines should be avoided • Sarilumab has no inhibitory or inducing effects on cytochromes. Sarilumab is expected to normalise cytochrome activity (via inhibition of IL-6) in patients with COVID-19 who experience an elevation of IL-6, which has been shown to suppress activity of drug metabolising enzymes, namely CYP3A4, but also others. This indirect effect of sarilumab on CYP450 enzyme activity may persist for several weeks after administration • For a full list of drug interactions check the University of Liverpool COVID-19 resource page
Presentation and storage	• Available as single use pre-filled injection syringe (PFS) delivering 200 mg per 1.14 mL of sarilumab (175 mg/mL)

	• Refrigerate vials at 2–8°C. Do not freeze
Dose	• 400 mg as a single dose via intravenous infusion over 60 minutes. Sarilumab can be given via a peripheral or central line

Administration	• Sarilumab comes as a subcutaneous pre-filled syringe (PFS). An intravenous (IV) formulation is not commercially available.
	  ◦ Add the sarilumab dose (400 mg/2.28 mL) from 2 pre-filled 200 mg syringes (PFS) to a 100 mL **Fresenius Kabi Sodium Chloride 0.9% Freeflex®**** 100 mL bag.
	  ◦ Invert gently 10 times when mixing to avoid foaming. Do NOT shake. Inspect the bag, which must be clear to opalescent, colourless to pale yellow and free from visible particles
	  ◦ Infusion set must contain a 0.2micron in-line filter
	  ◦ Do not use the same IV line to administer other medications at the same time
	  ◦ Prime the line with the sarilumab infusion. Infuse intravenously as follows:
	  ▪ 10mL per hour for 15 minutes then
	  ▪ Increase to 130mL per hour for at least 45 minutes until the bag is empty
	  ◦ After the sarilumab infusion is completed, run at least 20mL of sodium chloride 0.9% at 130mL per hour to flush the giving set.
	
	** The PFS needle (0.5 inch) may be too short to pierce the internal septum of the other brands of sodium chloride 0.9% infusion bags. The Fresenius Kabi Sodium Chloride 0.9% Freeflex® 100 mL bag allows the full dose of sarilumab to be injected into the additive port from the PFS. These are available in ICU (4G)

Monitoring	• Observe for hypersensitivity reaction during and for 30 minutes after the IV infusion. Resuscitation facilities must be readily available • Monitor for adverse effects by performing baseline and daily: complete blood exam (specifically neutrophils and platelets), and electrolytes, creatinine, urea, LFTs (transaminases and bilirubin) and CRP • New onset abdominal pain or concerns • Baseline testing for hepatitis B, HIV, HCV should be undertaken for all patients and consider strongyloides and tuberculosis testing according to epidemiological risk factors. Sarilumab treatment should **NOT** be delayed pending results of baseline tests
Adverse Effects	• As the proposed use is off-label, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use • Common (> 1%): Infections (including opportunistic), neutropenia, thrombocytopenia, leukopenia, injection site reactions (e.g. erythema and pruritus), increased liver enzymes, increased serum cholesterol and triglycerides, headache, diarrhoea. • Infrequent (0.1–1%): GI perforation, hypersensitivity reactions (e.g. urticaria, angioedema). • Rare (< 0.1%): Malignancy • 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	• Sarilumab patient information leaflets are available via the NSW Therapeutic Advisory Group • Example patient consent forms can be found here

Tocilizumab[1,2,3,5,7,8,9,11,16,17,19,20] **ID approval and patient consent (verbal or written) required** **For more detailed information on the use of tocilizumab in patients with COVID-19 visit the product information available on the TGA website**	
Drug Class	○ Anti-rheumatic, cytokine modulator, monoclonal antibody (humanised)
Indications	○ Off-label use of tocilizumab may be considered for patients with a current diagnosis of COVID-19, who require supplemental oxygen, particularly where there is evidence of systemic inflammation such as: ▪ Elevated ESR, C-reactive protein (CRP, D-dimers, lactate dehydrogenase, ferritin) • There is currently a critical shortage of tocilizumab and use should be limited to: ▪ Pregnant women ▪ Breastfeeding women ▪ Children and adolescents < 16 years old requiring supplemental oxygen ▪ Critically ill patients requiring direct admission to ICU for mechanical ventilation who are unable or contraindicated from having sarilumab • Unless corticosteroids are contraindicated (see dexamethasone monograph above), tocilizumab should be given in conjunction with dexamethasone for patients
Contraindications	• Hypersensitivity to any component of the product, Chinese hamster ovary cell products or other recombinant human or humanised antibodies. • Sepsis or active, severe infections from non-COVID-19 pathogens • Live and live-attenuated vaccines should not be given concurrently
Precautions	• A history of anaphylaxis to other medicines • A history of recurring or chronic infection, or with underlying conditions (e.g. diabetes) which may predispose patients to infections. • A history of HIV, positive core antibody for hepatitis B, prior HCV infection or symptomatic EBV infection • A history of tuberculosis/tuberculosis exposure • Concurrent immunosuppressive/anti-rejection therapy increases the risk of infection and should be avoided. • In patients with haematological abnormalities including the possibility of macrophage activation syndrome (MAS) or haemophagocytic lymphohistiocytosis, advice from a haematologist should be sought especially in those with ○ Absolute neutrophil count < 2 x 10^9/L ○ Platelets < 100 x 10^9/L • Active hepatic disease or hepatic impairment including abnormal liver enzymes (transaminases 3–5 times the upper limit of normal) • Patients with current or previous history of diverticulitis or intestinal ulceration
Drug Interactions	• Concurrent immunosuppressive/anti-rejection therapy increases the risk of infection and should be avoided.

	• Tocilizumab has no inhibitory or inducing effects on cytochromes. However, patients with COVID-19 may experience an elevation of IL-6, which has been shown to suppress activity of drug metabolising enzymes, namely CYP3A4, but also others. Tocilizumab will normalise cytochrome activity (via inhibition of IL-6). • The indirect effect of tocilizumab on CYP450 enzyme activity in this setting is unknown but the effects may persist for several weeks after administration. • Specialist input should be obtained regarding timing of future vaccinations. Live and live-attenuated vaccines should be avoided for 6 months • For a full list of drug interactions check the University of Liverpool COVID-19 resource page
Presentation and storage	Available as: • 80 mg/4 mL concentrate solution for IV infusion vial • 200 mg/10 mL concentrate solution for IV Infusion vial • 400 mg/20 mL concentrate solution for IV Infusion vial Store vials at 2–8°C. (Refrigerate. Do not freeze.)
Dose	• The suggested dose is dependent on actual body weight (for pregnant women use the weight at the time of clinical need): • Patients > 90 kg: 800 mg IV single dose • Patients > 65 and ≤ 90 kg: 600 mg IV single dose • Patients > 40 and ≤ 65 kg: 400 mg IV single dose • Patients ≤ 40 kg: 8 mg/kg IV single dose These dosing ranges are based on the doses used in the REMAP-CAP trial[17]
Administration	• Administer as a single intravenous infusion over 60 minutes 1. Ascertain the volume of tocilizumab solution that will be required and withdraw the same volume from a 100mL sodium chloride 0.9% infusion bag 2. Withdraw the tocilizumab dose from the vial(s) & add to the sodium chloride 0.9% infusion bag 3. Invert gently when mixing to avoid foaming. Do NOT shake. Inspect the bag, which must be clear to opalescent, colourless to pale yellow and free from visible particles. 4. Do not use the same IV line to administer other medications at the same time 5. Prime the line with tocilizumab infusion and then infuse intravenously over 60 minutes via either a central or peripheral line 6. After completion of the tocilizumab infusion, at least 20mL of 0.9% sodium chloride should be used to flush the giving set
Monitoring	• Monitor for adverse effects by performing including complete blood exam and electrolytes, creatinine, urea, LFTs and CRP (tocilizumab inhibits the production of CRP therefore a reduction in CRP should not be used as a marker of clinical improvement). • New onset gastrointestinal symptoms • Observe for hypersensitivity reaction during, and for 30 minutes after IV infusion. Resuscitation facilities must be readily available • Baseline testing for hepatitis B, HIV, HCV should be undertaken for all patients and consider strongyloides and tuberculosis testing according to epidemiological risk factors. Tocilizumab treatment should **NOT** be delayed pending results of baseline tests

Adverse Effects	• As tocilizumab is provisionally registered by the TGA for use in patients with COVID-19, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use • Common (>1%): Infections (including opportunistic), neutropenia, hypofibrinogenaemia, increased liver enzymes, gastritis, mouth ulcers, hypertension, infusion-related reactions (below), antibodies to tocilizumab, rash, itch, headache, dizziness • Infrequent (0.1–1%): GI perforation (possibly dose-related), thrombocytopenia, hypersensitivity reactions (e.g. urticaria, angioedema), dyspnoea, cough, conjunctivitis • Rare (<0.1%): Serious hepatotoxicity (including acute liver failure, hepatitis and jaundice, in some rare cases treatment has required liver transplant), pancreatitis, pulmonary fibrosis • Infusion-related reactions: Occur within 24 hours of IV infusion; they include hypertension, headache, rash, hypersensitivity (anaphylaxis 0.2%). • 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	• Tocilizumab patient information leaflets are available via the NSW Clinical Excellence Commission

Sotrovimab [1,2,3,4,6,7,9,10,13,33]

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	• Prescribed 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 Clinical Excellence Commission
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 patient information leaflets for sotrovimab can be found here • Sotrovimab patient information leaflets are available via the NSW Clinical Excellence Commission

DEFINITIONS/ACRONYMS/ABBREVIATIONS

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CRP	C-Reactive Protein
EBV	Epstein Barr Virus
ECMO	Extracorporeal membrane oxygenation
eGFR	estimated Glomerular Filtration Rate
ESR	Erythrocyte Sedimentation Rate
GI	Gastrointestinal
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IV	Intravenous
LFTs	Liver Function Tests
NMS	National Medical Stockpile
PFS	Prefilled syringe
SBECD	Sulfobutyl betadex sodium
ULN	Upper Limit of Normal
VTE	Venous Thromboembolism

LINKS TO RESOURCES

- National COVID-19 Clinical Evidence Taskforce (The Australian Living Guidelines)
- COVID-19 Resources: NSW Therapeutic Advisory Group
- IPCU: COVID–19 (SARS–COV–2) – Management Guide (CALHN–PRC05409)
- Anaphylaxis: Management Guidelines (CALHN-OWI04038)
- CALHN COVID–19 internet page
- World Health Organisation. Therapeutics and COVID-19: Living Guideline

- Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. 2020.
- Australian Technical Advisory Group on Immunisation (ATAGI)
- Clinical Excellence Commission: Medication Safety Updates
- COVID-19: Medication Management of mild illness in the outpatient setting (CALHN-GDE05808)

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