COVID-19 Treatment Guidelines for mild-moderate disease (Adults)

Department of Health

July 2022
About this document

This document has been developed by the Queensland Health COVID-19 Therapeutics Working Group to provide clinicians with recommendations on the treatment options for mild to moderate COVID-19 in adult patients (>18 years). For guidance in the management of children with COVID-19, refer to the CHQ Paediatric Guideline.

These guidelines are based on the recommendations of the Pharmaceutical Benefits Scheme (PBS) National COVID-19 Clinical Evidence Taskforce (NCCET), and the NIH (US) and NICE (UK) guidelines; they will be updated frequently as new evidence is made available.
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1. Classification of severity

Disease definitions according to by the Australian National COVID-19 Taskforce and World Health Organisation (WHO) living guidelines.

For patients with severe to critical disease, see the COVID-19 Treatment Guidelines for severe and critical disease (hospitalised adults).

1.1 Mild disease
- Patients with confirmed COVID-19 without evidence of viral pneumonia or hypoxia

1.2 Moderate disease
- Patients with confirmed COVID-19 with signs of pneumonia including SOB, tachypnoea, or cough without features of severe pneumonia (oxygen saturation ≥ 93% and < 95% on room air (RA))
- Desaturation or breathlessness with mild exertion
- Imaging may be required to confirm the diagnosis of pneumonia

1.3 Severe disease
- Patients with confirmed COVID-19 with signs of severe pneumonia who are deteriorating
- Respiratory rate (RR) ≥ 30 breaths per minute
- Oxygen saturation ≤ 92% RA and/or requiring oxygen supplementation
- Lung infiltrates ≥ 50% on imaging

1.4 Critical COVID-19 infection
Defined as patients with respiratory tract infections progressing to respiratory failure, septic shock, or severe organ dysfunction
- Acute Respiratory Distress Syndrome (ARDS)
  - Onset usually within a week of respiratory symptoms
  - Bilateral opacities not explained by other aetiology
  - Oxygenation impairment (mild, moderate, or severe based on PaO₂/FiT consults)
• Life-threatening organ dysfunction/failure
• Impairment of consciousness
• Septic Shock
  o Sepsis with persistent hypotension despite volume resuscitation.

2. Treatment

2.1 Treatment principles

COVID-19 therapies other than those listed in this document should be prescribed only in the context of a clinical trial.

Current standard of care therapy for patients with mild to moderate disease may include:

1. Anti-spike monoclonal antibodies (e.g. sotrovimab, tixagevimab and cilgavimab, casirivimab and imdevimab^)
2. Anti-viral therapy (e.g. nirmatrelvir plus ritonavir, molnupiravir, remdesivir)
3. Inhaled corticosteroids (budesonide).

^Current evidence suggests that casirivimab plus imdevimab does not neutralise the Omicron strain of the SARS-CoV-2 virus. It should not be used unless genotyping confirms infection with an alternate strain.¹
3. Overview of therapeutics for mild-moderate disease

3.1 Budesonide (inhaled)

Budesonide currently has a conditional recommendation by the Australian National COVID-19 Taskforce. It is not recommended in the NICE Guidelines (UK) or NIH Guidelines (US) outside of a clinical trial. There is significant uncertainty over current clinical benefit and limited access in Queensland.²

Indications

- Mild or moderate COVID-19 patients who do not require oxygen supplementation with risk factors for disease progression:
  - Diabetes (use with caution and monitor blood glucose levels)
  - Heart disease and/or hypertension
  - Asthma or lung disease
  - Weakened immune system due to a serious illness or medication (e.g. chemotherapy)
  - Mild hepatic impairment
  - Stroke or other neurological problem

Dose and duration

- 800 mcg inhaled TWICE DAILY until symptom resolution, up to 14 days. (Use Pulmicort Turbuhaler® 400 mcg/dose: 2 inhalations TWICE daily) Nebulised administration is not recommended.

- For advice on how to use a Turbuhaler—see here.

3.2 Anti-spike monoclonal antibodies

3.2.1 Sotrovimab

Sotrovimab is a recombinant human immunoglobulin monoclonal antibody targeting the spike protein receptor binding domain of SARS-CoV-2. The COMET-ICE trial demonstrated efficacy and safety data in 291 patients in the sotrovimab treatment arm.³ A single 500 mg COVID-19 Treatment Guidelines for mild-moderate disease (Adults) v1.5 Published 28/07/2022 Page 8 of 35
infusion of sotrovimab was found to decrease the risk of hospitalisation if given within 5 days of symptom onset in non-hospitalised, partially or unvaccinated patients with confirmed COVID-19 who did not require oxygen and were at high risk of medical complications compared to placebo. The number needed to treat with sotrovimab to prevent one hospitalisation event is approximately 16.

Efficacy against Omicron sub-strains may be reduced. The situation is being monitored and as further data emerges these recommendations will be revised as necessary. Current data supports the efficacy of sotrovimab against Omicron BA.1 and BA.1.1 sublineages, but it is advised that there is uncertainty of effectiveness of the 500mg dose against Omicron BA.2 sublineage. In April 2022, the sponsor GlaxoSmithKline (GSK) Australia Pty Ltd applied to the TGA for registration of a higher dose (1000mg) to combat infection by the Omicron BA.2 sublineage. This application is currently under assessment by the TGA.

For further information, see the Sotrovimab prescribing guideline, available on the COVID-19 Clinical guidelines page.

3.2.2 Tixagevimab and cilgavimab (Evusheld®)

Tixagevimab and cilgavimab is a recombinant human immunoglobulin monoclonal antibody combination targeting two distinct sites on the spike protein receptor binding domain of SARS-CoV-2. Tixagevimab and cilgavimab is primarily used for prophylaxis in patients who are at high risk of severe COVID-19 infection due to immunosuppressive conditions that confers a poor immune response to vaccination or patients who have conditions that preclude the administration of COVID-19 vaccinations.

Patients who are eligible to receive tixagevimab and cilgavimab according to the priority tiers (found in the tixagevimab and cilgavimab guidelines) but become infected with the SARS-CoV-2 virus and present with asymptomatic, mild or moderate infection are eligible for early treatment. The dose for early treatment is 300/300mg.

This recommendation is based on results of the TACKLE trial. TACKLE is a Phase III randomised, double-blind, placebo-controlled, multi-centre trial assessing the safety and efficacy of a single 600 mg IM dose compared to placebo for the outpatient treatment of COVID-19. The 903 participants were non-hospitalised adults with mild-to-moderate COVID-19 who were within 7 days of symptom onset and had one or more risk factors for progression to severe disease. The primary efficacy endpoint was the composite of either
severe COVID-19 or death from any cause through day 29. Tixagevimab and cilgavimab probably reduces progression to severe disease or death (RR 0.50, CI 95% 0.29, 0.86).

Patients who have received tixagevimab and cilgavimab for prophylaxis within 6 months of a COVID-19 infection should be considered for antiviral therapy.

### 3.2.3 Casirivimab and imdevimab (Ronapreve®)

Casirivimab and imdevimab is a recombinant human immunoglobulin monoclonal antibody combination targeting two distinct sites on the spike protein receptor binding domain of SARS-CoV-2. It may be used as an alternative to sotrovimab, particularly those at day 5 – 7 from symptom onset. Sotrovimab is the preferred monoclonal antibody due to ease of administration and activity against the Omicron strain. The REGEN-COV study demonstrated efficacy of both 600mg/600mg and 1200mg/1200mg doses with an overall 2.2% absolute reduction and 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.\(^5\)

**NOTE:** Current evidence suggests that casirivimab and imdevimab does not neutralise the Omicron strain (and sub-strains of Omicron) of the SARS-CoV-2 virus. It should not be used unless genotyping confirms infection with an alternate strain\(^1\)

For further information, see the [casirivimab and imdevimab prescribing guideline](#).

### 3.3 Anti-viral therapy

#### 3.3.1 Nirmatrelvir plus ritonavir (Paxlovid®)

Nirmatrelvir is a peptidomimetic that inhibits the 3C-like protease, rendering it incapable of processing polyprotein precursors, thus preventing viral replication. It is administered orally in combination with low-dose ritonavir (which inhibits the CYP3A-mediated metabolism of nirmatrelvir) to maintain adequate plasma levels of nirmatrelvir.\(^6\) Efficacy was demonstrated in the EPIC-HR trial with an absolute risk reduction of 5.81% or an 88.9% relative risk reduction in the primary endpoints of COVID-19 related hospitalisation or death from any cause in participants who received treatment within 3 days of symptom onset.\(^7\)

Nirmatrelvir/ritonavir was listed on the Pharmaceutical Benefits Scheme on May 1\(^{st}\), 2022, with a streamlined authority for the treatment of SARS-CoV-2 infection. Under the PBS criteria patients aged 70 years or older, or 50 years and older (≥30 years if Aboriginal and Torres Strait Islander) and have at least two or more risk factors for progression to severe COVID-19.
disease (regardless of vaccination status), can be prescribed nirmatrelvir/ritonavir. For patients who are admitted to Hospital and Health Service virtual wards, prescribing may occur according to the PBS criteria but access to the medication is provided through the national medicines stockpile.

For further information, refer to the nirmatrelvir plus ritonavir prescribing guideline.

3.3.2 Molnupiravir

Molnupiravir is an oral pro-drug that is hydrolysed to a ribonucleoside analogue. It subsequently misdirects the viral polymerase, resulting in viral mutations and lethal mutagenesis.\(^8\) Safety and efficacy was demonstrated in the MOVe-OUT trial, where in the final analysis of 1,433 participants, there was a 30% relative risk reduction in the primary composite outcome of death or all-cause hospitalisation in participants receiving treatment within 5 days of symptom onset.\(^9\)

Molnupiravir was listed on the Pharmaceutical Benefits Scheme on March 1\(^{st}\), 2022, with a streamlined authority for the treatment of SARS-CoV-2 infection. Under the PBS criteria patients aged 70 years or older, or 50 years and older (≥30 years if Aboriginal and Torres Strait Islander) and have at least two or more risk factors for progression to severe disease (regardless of vaccination status), can be prescribed molnupiravir. For patients who are admitted to Hospital and Health Service virtual wards, prescribing may occur according to the PBS criteria but access to the medication is provided through the national medicines stockpile.

For further information, refer to the molnupiravir prescribing guideline.

3.3.3 Remdesivir

Remdesivir is a nucleotide prodrug of an adenosine analogue, given intravenously. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely.\(^10\) Efficacy in the treatment of early mild to moderate disease was demonstrated in the PINETREE trial. Non-hospitalised high-risk patients with COVID-19 who were treated with a three-day course of remdesivir within 7 days of symptom onset, had an 87% relative reduction in the risk of hospitalisation or death.\(^11\)

For further information, refer to the remdesivir prescribing guideline.
4. Therapeutic approach

Given its lack of activity versus the Omicron variant, casirivimab and imdevimab has limited utility in the current Omicron wave and will not be discussed further in this guideline. As new variants arise, the preference of treatments is likely to change.

4.1 First line therapy

- nirmatrelvir/ritonavir (Paxlovid®) OR molnupiravir
- remdesivir (where 3 days of IV therapy is feasible)
- Tixagevimab and cilgavimab or sotrovimab (anti-spica mAB) as an alternative for patients meeting the priority access criteria

4.2 Second line therapy

Prescribing guidelines are available for each therapeutic agent and should be consulted for detailed advice.

**Table 1: Recommended drug doses**

<table>
<thead>
<tr>
<th></th>
<th>Standard dose</th>
<th>Renally adjusted dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molnupiravir</td>
<td>800 mg (4 x 200 mg capsules) orally 12-hourly for 5 days</td>
<td>No dose adjustment necessary in mild, moderate or severe renal impairment</td>
</tr>
<tr>
<td>Nirmatrelvir/ritonavir</td>
<td>eGFR &gt; 60 mL/min 300 mg nirmatrelvir (2 tablets) plus 100 mg ritonavir (1 tablet) orally 12-hourly for 5 days</td>
<td>eGFR ≤ 60 and ≥ 30 mL/min 150 mg nirmatrelvir (1 tablet) plus 100 mg ritonavir (1 tablet) orally 12-hourly for 5 days</td>
</tr>
<tr>
<td></td>
<td>eGFR &lt; 30 mL/min including dialysis:</td>
<td>eGFR &lt; 30 mL/min including dialysis:</td>
</tr>
<tr>
<td></td>
<td>Day 1: 300mg nirmatrelvir (2 tablets) plus 100mg ritonavir (1 tablet) orally, ONCE daily.</td>
<td>Day 1: 300mg nirmatrelvir (2 tablets) plus 100mg ritonavir (1 tablet) orally, ONCE daily.</td>
</tr>
<tr>
<td></td>
<td>Day 2 to 5: 150mg nirmatrelvir (1 tablet) plus ritonavir (1 tablet) orally, ONCE daily.</td>
<td>Day 2 to 5: 150mg nirmatrelvir (1 tablet) plus ritonavir (1 tablet) orally, ONCE daily.</td>
</tr>
<tr>
<td></td>
<td>Standard dose</td>
<td>Renally adjusted dose</td>
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<td>----------------------</td>
<td>----------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In patients on renal replacement therapy, dose should be given after dialysis</td>
</tr>
<tr>
<td>Remdesivir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>eGFR ≥ 30 mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg IV loading dose on day 1, then 100 mg IV daily on day 2 and 3 (maximum of 3 days treatment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eGFR &lt; 30 mL/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not requiring dialysis:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200mg IV loading dose once on day 1, then 100mg IV once on day 2, no further doses needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Requiring dialysis:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg IV loading dose on day 1, then 100 mg IV daily on day 2 and 3. Give dose 4 hours before dialysis or any time after.</td>
<td></td>
</tr>
<tr>
<td>Tixagevimab and</td>
<td>300/300 mg as a single intramuscular dose</td>
<td>No dose adjustment necessary in mild, moderate or severe renal impairment</td>
</tr>
<tr>
<td>cilgavimab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotrovimab</td>
<td>500 mg as a single dose by intravenous infusion (1000mg dose is under review by the TGA, refer to information in 3.2.1)</td>
<td>No dose adjustment necessary in mild, moderate or severe renal impairment</td>
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</tbody>
</table>
4.3 Rationale

Recommendations for the use of nirmatrelvir/ritonavir, molnupiravir, remdesivir and sotrovimab have been formulated according to the Pharmaceutical Benefits Scheme (PBS), Australian National COVID-19 Taskforce, National Institute of Health (NIH) and the National Institute for Health and Care Excellence (NICE) guidelines. Due to uncertain benefit against SARS-CoV-2 variants of concern, sotrovimab will only be preferred as an option in pregnancy or for high risk patients who have contraindications to nirmatrelvir/ritonavir (Paxlovid) or molnupiravir (Lagevrio) and who do not meet priority criteria for tixagevimab and cilgavimab.

The MOVe-OUT study demonstrated efficacy of molnupiravir for preventing hospitalisation in patients with COVID-19 within 5 days of symptom onset and who have one or more risk factors for disease progression. Due to reduced efficacy of molnupiravir in the composite endpoint of hospitalisation or death for the final analysis compared with interim analysis in the MOVe-OUT study, along with limited evidence and safety data, molnupiravir should be considered where nirmatrelvir/ritonavir are not suitable or available. Remdesivir may be considered as an alternative but is limited in application due to an IV administration requirement for 3 consecutive days. For patients who are admitted to hospital with mild-moderate COVID, remdesivir is the preferred therapy.

4.3.1 Combination therapy

Although there is uncertain clinical benefit for combination therapy, clinicians may choose to combine an antiviral therapy with anti-SARS-CoV-2 monoclonal antibody therapy. Patients who are eligible to receive tixagevimab and cilgavimab or sotrovimab should also be considered for antiviral therapy.

Refer to the tixagevimab and cigavimab, nirmatrelvir/ritonavir, sotrovimab, remdesivir and molnupiravir guidelines for further details.
4.4 Special considerations

4.4.1 Pregnancy

Pregnancy by itself is not an immunosuppressive condition requiring COVID-19 therapeutics:

- Pregnant women with additional risk factors for COVID-19 disease progression should be managed as per the eligibility criteria in the table 3.
- Nirmatrelvir/ritonavir and molnupiravir are both contraindicated in pregnancy.
- Sotrovimab or tixagevimab and cilgavimab may be given in trimester two and three.
- Remdesivir is category B2 in pregnancy, from the limited data available, maternal use has not been associated with an increased risk of congenital malformations or adverse pregnancy outcomes.

5. Eligibility

5.1 Inclusion criteria

Apart for specific priority cohorts for tixagevimab and cilgavimab and sotrovimab, general criteria for treatment of mild to moderate disease are based on PBS criteria:

Non-hospitalised* patients with

- SARS-CoV-2 infection confirmed by either
  1. Polymerase chain reaction (PCR) testing OR
  2. Rapid antigen test (RAT)"

AND

- Symptomatic with (mild to moderate) COVID-19 (within 5 days^ of symptom onset)

AND

- Patient meets criteria for therapy:
  1. Non-immunosuppressed patient
     a. Age 70 years or older
     b. (Age ≥ 50 or age ≥ 30 if the patient identifies as Aboriginal or Torres Strait Islander and at least 2 of the following):
- The patient is in residential aged care or residential disability care
- The patient has a disability with multiple comorbidities and/or frailty
- Neurological conditions, including stroke, dementia, and demyelinating conditions
- Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease
- Congestive heart failure
- Obesity (BMI greater than 30 kg/m²),
- Diabetes Types I and II, requiring medication for glycaemic control
- Renal failure (eGFR less than 60mL/min)
- Cirrhosis
- The patient has 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

2. **Patients (≥18 years) with moderate to severe immunosuppression** defined as:
   a. Any primary or acquired immunodeficiency including:
      - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders
      - Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months),
      - Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
   b. Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received:
      - Chemotherapy or whole body radiotherapy
- High-dose corticosteroids (greater than or equal to 20 mg of prednisone per day, or equivalent) for at least 14 days in a month, or pulse corticosteroid therapy
- Biological agents and other treatments that deplete or inhibit B cell or T cell function (abatacept, anti-CD20 antibodies, BTK inhibitors, JAK inhibitors, sphingosine 1-phosphate receptor modulators, anti-CD52 antibodies, anti-complement antibodies, anti-thymocyte globulin)
- Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) including mycophenolate, methotrexate, leflunomide, azathioprine, 6-mercaptopurine (at least 1.5mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus)
  c. Any significantly immunocompromising condition(s) where, in the last 12 months the patient has received rituximab,
  d. Others with very high risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies
  e. People with disability with multiple comorbidities and/or frailty

*Patients hospitalised for a non-COVID indication not requiring oxygen due to COVID may be eligible.

^Patient self-administered RAT should be repeated by a Healthcare Worker.

Within 7 days, remdesivir can be considered.

In addition to this cohort, patients who are not up to date with vaccination and are under the age of 50 (or 30 if they identify as Aboriginal or Torres Strait Islander) with additional risk factors for severe COVID-19 disease (table 2) are eligible for oral antivirals as per the National COVID-19 task force recommendations. In this scenario, prescribing of oral antiviral therapy should occur through hospital pharmacies via NMS stockpiles.
5.2 Symptoms of COVID-19

Include any of: fever, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhoea, headache, red or watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomach-ache, rash, sneezing, sputum or phlegm, runny nose

5.4 Risk factors for severe disease

Table 2: Risk factors for severe disease

<table>
<thead>
<tr>
<th>Risk factors for severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥ 50 (or &gt; 30 if Aboriginal or Torres Strait Islander)</td>
</tr>
<tr>
<td>• Obesity (BMI ≥ 30 kg/m²)</td>
</tr>
<tr>
<td>• CKD (eGFR &lt; 60 mL/min/1.73m²)</td>
</tr>
<tr>
<td>• Serious cardiac condition (such as heart failure, coronary artery disease or cardiomyopathy)</td>
</tr>
<tr>
<td>• Pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, significant bronchiectasis or emphysema with dyspnoea on physical exertion)</td>
</tr>
<tr>
<td>• Moderate-to-severe asthma (requiring inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months)</td>
</tr>
<tr>
<td>• Diabetes mellitus (requiring medication)</td>
</tr>
</tbody>
</table>

• Other significant risk factors:
  o Medical related technologic dependence (BiPAP, other ventilation not related to COVID-19)
  o Neurodevelopment disorders (including cerebral palsy, Down’s syndrome etc)
  o Sickle cell disease
  o Patients with neuromuscular disease with respiratory muscle involvement (spinal cord injury, post-polio syndrome, SMA, motor neurone disease, Duchenne or other muscular dystrophy, myotonic dystrophy, myasthenia gravis)
- Very high risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies
- People with severe intellectual or physical disabilities requiring residential care
## 5.5 Recommended therapy

Table 3: Recommendations based on risk factors and immunosuppression status

<table>
<thead>
<tr>
<th>COHORT</th>
<th>Antiviral Therapy</th>
<th>mAB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirmatrelvir plus ritonavir</td>
<td>CONTRAINDICATED</td>
<td>CONSIDER</td>
</tr>
<tr>
<td>Molnupiravir</td>
<td>CONTRAINDICATED</td>
<td>PREFERRED FOR IMMUNOSUPPRESS ED PREGNANT PATIENTS WHO MEET PRIORITY CRITERIA FOR TIXAGEVIMAB and CILGAVIMAB (Trimester 2 and 3)</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>CONSIDER</td>
<td>PREFERRED FOR IMMUNOSUPPRESS ED PREGNANT PATIENTS WHO MEET PRIORITY CRITERIA FOR TIXAGEVIMAB and CILGAVIMAB (Trimester 2 and 3)</td>
</tr>
<tr>
<td>Tixagevimab and cilgavimab</td>
<td></td>
<td></td>
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<tr>
<td>Sotrovimab</td>
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<td></td>
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</tbody>
</table>

**Pregnant patients who:**

- Are not fully vaccinated AND with additional risk factors
- Are immunosuppressed regardless of vaccination status*

Should be considered for sotrovimab in the second and third trimesters^

*pregnancy itself is not considered an immunosuppressive condition

^use of sotrovimab in the first trimester may be considered in high-risk patients following a risk assessment, however risk to the foetus is unknown.
Patients who are eligible based on risk factors for severe disease (table 2) and according to PBS criteria

<table>
<thead>
<tr>
<th>COHORT</th>
<th>Antiviral Therapy</th>
<th>mAB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nirmatrelvir plus ritonavir</td>
<td>Molnupiravir</td>
</tr>
<tr>
<td>PREFERRED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Contraindicated in:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• severe hepatic impairment Child-Pugh Class C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• for other contraindications see the prescribing guideline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Clinically significant drug interactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>check COVID-19 drug interactions checker</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RECOMMENDED AS ALTERNATIVE

IF NIRMATRELVIR/RITONAVIR THERAPY NOT AVAILABLE OR CONTRAINDICATED

ALTERNATIVE

FOR PATIENTS HOSPITALISED FOR ANOTHER REASON OR WHERE IT IS FEASIBLE TO BE ADMINISTERED IN AN OUTPATIENT SETTING OVER 3 DAYS

NOT INDICATED

ALTERNATIVE

IF NIRMATRELVIR PLUS RITONAVIR or MOLNUPIRAVIR ARE CONTRAINDICATED AND IN SOTROVIMAB PRIORITY COHORT
<table>
<thead>
<tr>
<th>COHORT</th>
<th>Antiviral Therapy</th>
<th>mAB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis dependent patients</td>
<td>Nirmatrelvir plus</td>
<td>Tixagevimab and</td>
</tr>
<tr>
<td></td>
<td>ritonavir</td>
<td>cilgavimab</td>
</tr>
<tr>
<td>WITH an additional COVID-19 risk factors</td>
<td>Molnupiravir</td>
<td></td>
</tr>
<tr>
<td>for severe disease (as listed in table 2)</td>
<td>Remdesivir</td>
<td></td>
</tr>
<tr>
<td>CONSIDER</td>
<td>RECOMMENDED</td>
<td></td>
</tr>
<tr>
<td>DOSE ADJUSTMENT IS REQUIRED AND THERAPY</td>
<td>ALTERNATIVE</td>
<td>CONSIDER</td>
</tr>
<tr>
<td>SHOULD BE ADMINISTERED AFTER DIALYSIS</td>
<td></td>
<td>IF PATIENT IS SERONEGATIVE AT TIME OF COVID-19 DIAGNOSIS AND PATIENT HAS RECEIVED 3 DOSE PRIMARY VACCINATION COURSE IN ADDITION TO ANTIVRAL THERAPY</td>
</tr>
<tr>
<td>CONSIDER</td>
<td></td>
<td>IF PATIENT IS SEROPositive AT TIME OF DIAGNOSIS (OR IF SEROSTATUS IS UNKNOWN) IN ADDITION TO ANTIVRAL THERAPY</td>
</tr>
<tr>
<td>COHORT</td>
<td>Antiviral Therapy</td>
<td>mAB Therapy</td>
</tr>
<tr>
<td>--------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Patients on immunosuppressive therapy</strong> (no other risk factors required)</td>
<td>Nirmatrelvir plus ritonavir</td>
<td>Molnupiravir</td>
</tr>
<tr>
<td>• B or T cell depleting therapy within the previous 12 months (Rituximab, ocrelizumab, ofatumumab, alemtuzumab, venetoclax, Anti-Thymocyte globulin)</td>
<td>CONSIDER IN COMBINATION WITH mAB</td>
<td>CONSIDER IN COMBINATION WITH mAB</td>
</tr>
<tr>
<td>• CAR-T/NK cell immunotherapy within 12 months</td>
<td>Note: 1. Contraindicated in: severe hepatic impairment Child-Pugh Class C</td>
<td>IF NIRMATRELVIR/RIPTONAVIR THERAPY NOT AVAILABLE OR CONTRAINDICATED</td>
</tr>
<tr>
<td>• Ibrutinib, acalabrutinib, zanubrutinib within 6 months</td>
<td>2. Clinically significant drug interactions. check <a href="#">COVID-19 drug interactions checker</a></td>
<td></td>
</tr>
<tr>
<td>• High dose (&gt; 1 g/m²) cyclophosphamide within previous 12 months</td>
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### COHORT

<table>
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<tr>
<th>Other immunosuppressive therapy: (no other risk factors required)</th>
<th>Antiviral Therapy</th>
<th>mAB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirmatrelvir plus ritonavir</td>
<td>Molnupiravir</td>
<td>Remdesivir</td>
</tr>
<tr>
<td>PREFERRED</td>
<td>RECOMMENDED AS SECOND LINE</td>
<td>ALTERNATIVE</td>
</tr>
<tr>
<td>Note:</td>
<td>IF FIRST LINE THERAPY NOT AVAILABLE OR CONTRAINDICATED</td>
<td>FOR PATIENTS HOSPITALISED FOR ANOTHER REASON OR WHERE IT IS FEASIBLE TO BE ADMINISTERED IN AN OUTPATIENT SETTING OVER 3 DAYS</td>
</tr>
<tr>
<td>1. <strong>Contraindicated in:</strong></td>
<td></td>
<td>CONSIDER</td>
</tr>
<tr>
<td>- severe hepatic impairment Child-Pugh Class C</td>
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<tr>
<td>- for other contraindications see the <a href="#">prescribing guideline</a></td>
<td></td>
<td>ALTERNATIVE FOR PATIENTS UNABLE TO BE PRESCRIBED ORAL ANTIVIRAL THERAPY</td>
</tr>
<tr>
<td>2. Clinically significant drug interactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>check <a href="#">COVID-19 drug interactions checker</a></td>
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<td></td>
</tr>
</tbody>
</table>

**Note:**

1. Contraindicated in:
   - severe hepatic impairment Child-Pugh Class C
   - for other contraindications see the [prescribing guideline](#)

2. Clinically significant drug interactions.
   - check [COVID-19 drug interactions checker](#)

**Other immunosuppressive therapies:**

- JAK inhibitors: baricitinib, tofacitinib, upadacitinib
- Daratumumab within 6 months
- Ruxolitinib within 6 months
- Bortezomib / carfilzomib
- Lenalidomide / pomalidomide
- TKIs and other targeted therapies (dasatinib, nilotinib, imatinib, osimertinib, erlotinib, crizotinib, alectinib, lorlatinib, etc)
- Complement inhibitors (eculizumab)
- Anti-TNF (infliximab, adalimumab, etanercept, golimumab, certolizumab) or Anti-IL-6 (tocilizumab) when used in combination with other DMARDs
- S1PR modulators (fingolimod, siponimod)
- Belimumab

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<tr>
<th>COHORT</th>
<th>Nirmatrelvir plus ritonavir</th>
<th>Molnupiravir</th>
<th>Remdesivir</th>
<th>Tixagevimab and cilgavimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other immunosuppressive therapy (Not malignancy or solid organ transplant indication)</strong>&lt;br&gt;(no other risk factors required)</td>
<td><strong>Caution Advised</strong>&lt;br&gt;Contact treating physician – do not commence without discussion&lt;br&gt;Note: 1. <strong>Contraindicated in:</strong>&lt;br&gt;• severe hepatic impairment Child-Pugh Class C&lt;br&gt;• for other contraindications see the <a href="#">prescribing guideline</a>&lt;br&gt;2. Clinically significant drug interactions.&lt;br&gt;check COVID-19 drug interactions checker</td>
<td><strong>RECOMMENDED AS SECOND LINE</strong>&lt;br&gt;IF FIRST LINE THERAPY NOT AVAILABLE OR CONTRAINDED</td>
<td><strong>ALTERNATIVE</strong>&lt;br&gt;FOR PATIENTS HOSPITALISED FOR ANOTHER REASON OR WHERE IT IS FEASIBLE TO BE ADMINISTERED IN AN OUTPATIENT SETTING OVER 3 DAYS</td>
<td><strong>CONSIDER</strong>&lt;br&gt;IF PATIENT IS SERONEGATIVE AT TIME OF DIAGNOSIS AND PATIENT HAS RECEIVED 3 DOSE PRIMARY VACCINATION COURSE</td>
<td><strong>ALTERNATIVE</strong>&lt;br&gt;FOR PATIENTS UNABLE TO BE PRESCRIBED ORAL ANTIVIRAL THERAPY</td>
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<td>COHORT</td>
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<td>Sotrovimab</td>
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<tr>
<td><strong>Transplantation:</strong></td>
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<tr>
<td>(no other risk factors required)</td>
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<tr>
<td>• Lung transplant recipient (anytime)</td>
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<tr>
<td>• Solid organ transplant recipient within 1 year (not lung transplant)</td>
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<tr>
<td>• Allogeneic stem cell transplantation within 1 year or on immunosuppression / chronic GVHD</td>
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<tr>
<td>• Autologous stem cell transplantation within 6 months</td>
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</tr>
<tr>
<td><strong>Caution Advised</strong></td>
<td>CONTACT Transplant Physician – do not commence without discussion</td>
<td>CONTACT Transplant Physician</td>
<td>PREFERRED AS PER TIXAGEVIMAB and CILGAVIMAB PRIORITY COHORT. REFER TO ACCESS CRITERIA</td>
<td>ALTERNATIVE FOR PATIENTS UNABLE TO BE ADMINISTERED TIXAGEVIMAB and CILGAVIMAB</td>
<td></td>
</tr>
<tr>
<td>Note:</td>
<td>1. Contraindicated in:</td>
<td>IN COMBINATION WITH mAB</td>
<td>2. Clinically significant drug interactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• severe hepatic impairment Child-Pugh Class C</td>
<td></td>
<td>• check COVID-19 drug interactions checker</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• for other contraindications see the prescribing guideline</td>
<td></td>
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</tbody>
</table>
## Antiviral Therapy

<table>
<thead>
<tr>
<th>COHORT</th>
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<tbody>
<tr>
<td>Nirmatrelvir plus ritonavir</td>
<td>Molnupiravir</td>
<td>Remdesivir</td>
</tr>
<tr>
<td>• Use with caution in patients on calcineurin inhibitors or mTOR inhibitors</td>
<td>CONTACT Transplant Physician – do not commence without discussion</td>
<td>CONTACT Transplant Physician</td>
</tr>
<tr>
<td><strong>Caution Advised</strong></td>
<td>CONTACT Transplant Physician PREFERRED</td>
<td>CONTACT Transplant Physician ALTERNATIVE</td>
</tr>
</tbody>
</table>

### Transplantation:

(no other risk factors required)

- Solid organ transplantation on immunosuppression greater than 1 year (not lung transplant recipient)
- Allogeneic stem cell transplantation greater than 1 year and within 2 years
- Autologous stem cell transplantation greater than 6 months and within 12 months

**Note:**

1. **Contraindicated in:**
   - severe hepatic impairment Child-Pugh Class C
   - for other contraindications see the prescribing guideline

CONSIDER IF PATIENT IS KNOWN TO BE SERONEGATIVE AT TIME OF COVID-19 DIAGNOSIS AND PATIENT HAS RECEIVED 3 DOSE PRIMARY VACCINATION COURSE

CONSIDER IF PATIENT IS SEROPOSITIVE AT TIME OF DIAGNOSIS (OR IF SEROSTATUS IS UNKNOWN)
<table>
<thead>
<tr>
<th>COHORT</th>
<th>Antiviral Therapy</th>
<th>mAB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nirmatrelvir plus ritonavir</td>
<td>Molnupiravir</td>
</tr>
</tbody>
</table>
|        | **2. Clinically significant drug interactions.**  
  - check [COVID-19 drug interactions checker](#)  
  Use with caution in patients on calcineurin inhibitors or mTOR inhibitors | | SETTING OVER 3 DAYS | | |
<table>
<thead>
<tr>
<th>COHORT</th>
<th>Antiviral Therapy</th>
<th>mAB Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunodeficiency disorders: (no other risk factors required)</td>
<td>Nirmatrelvir plus ritonavir</td>
<td>Molnupiravir</td>
</tr>
<tr>
<td>• Major antibody deficiency (i.e. CVID or XLA)</td>
<td>PREFERRED Note: 1. Contraindicated in: severe hepatic impairment Child-Pugh Class C for other contraindications see the prescribing guideline 2. Clinically significant drug interactions. check COVID-19 drug interactions checker 3. Contraindicated in: HIV positive patients with HIV viral load &gt; 400 copies/mL</td>
<td>RECOMMENDED AS SECOND LINE IF FIRST LINE THERAPY NOT AVAILABLE OR CONTRAINDED</td>
</tr>
<tr>
<td>COHORT</td>
<td>Antiviral Therapy</td>
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</tr>
<tr>
<td>--------</td>
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<td>-------------</td>
</tr>
<tr>
<td>Immunodeficiency disorders: (no other risk factors required)</td>
<td></td>
<td></td>
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<tr>
<td>• Aplastic anaemia on active therapy</td>
<td></td>
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<tr>
<td>• Primary immunodeficiency syndromes where immunoglobulin replacement is required (excluding specific antibody deficiency)</td>
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</tr>
<tr>
<td>• Secondary hypogammaglobulinemia requiring immunoglobulin replacement – risk related to underlying therapy / disease resulting in 2nd hypogammaglobulinemia</td>
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</tr>
<tr>
<td>• HIV positive (CD4 &gt; 50 cells/mm³)</td>
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</tr>
</tbody>
</table>

**PREFERRED**

Note: 1. **Contraindicated in:**
- severe hepatic impairment Child-Pugh Class C
- for other contraindications see the [prescribing guideline](#)

2. **Clinically significant drug interactions.**
- check COVID-19 drug interactions checker

3. **Contraindicated in:** HIV positive patients with HIV viral load > 400 copies/mL

**RECOMMENDED AS SECOND LINE**

IF FIRST LINE THERAPY NOT AVAILABLE OR CONTRAINDED

**ALTERNATIVE**

FOR PATIENTS HOSPITALISED FOR ANOTHER REASON OR WHERE IT IS FEASIBLE TO BE ADMINISTERED IN AN OUTPATIENT SETTING OVER 3 DAYS

**CONSIDER**

IF PATIENT IS KNOWN TO BE SERONEGATIVE AT TIME OF COVID-19 DIAGNOSIS AND PATIENT HAS RECEIVED 3 DOSE PRIMARY VACCINATION COURSE

**CONSIDER**

IF PATIENT IS SEROPOSITIVE AT TIME OF DIAGNOSIS (OR IF SEROSTATUS IS UNKNOWN)
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<tr>
<th>COHORT</th>
<th>Antiviral Therapy</th>
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<tbody>
<tr>
<td>Haematologic malignancy on active therapy</td>
<td>Nirmatrelvir plus ritonavir</td>
<td>Tixagevimab and cilgavimab</td>
</tr>
<tr>
<td></td>
<td>Molnupiravir</td>
<td>Sotrovimab</td>
</tr>
<tr>
<td></td>
<td>Remdesivir</td>
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</table>

**PREFERRED**

**RECOMMENDED AS SECOND LINE**

**ALTERNATIVE**

**Note:**

1. **Contraindicated in:**
   - severe hepatic impairment Child-Pugh Class C
   - for other contraindications see the prescribing guideline

2. **Clinically significant drug interactions:**
   - check COVID-19 drug interactions checker

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**FOR PATIENTS HOSPITALISED FOR ANOTHER REASON OR WHERE IT IS FEASIBLE TO BE ADMINISTERED IN AN OUTPATIENT SETTING OVER 3 DAYS**

**FOR PATIENTS UNABLE TO BE ADMINISTERED TIXAGEVIMAB and CILGAVIMAB**
## Antiviral Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Nirmatrelvir plus ritonavir</th>
<th>Molnupiravir</th>
<th>Remdesivir</th>
<th>Tixagevimab and cilgavimab</th>
<th>Sotrovimab</th>
</tr>
</thead>
</table>

### Chemotherapy / malignancy

- Acute myeloid leukaemia induction / consolidation within 6 months
- Acute lymphoblastic leukaemia induction / consolidation / maintenance within 12 months
- Lung cancer on active chemotherapy +/- immunotherapy within 6 months
- Other malignancies (both haematological and solid cancer): moderate intensity chemotherapy within 2 weeks
- Recent whole-body radiotherapy or total lymphoid irradiation

**PREFERRED**

**Contraindicated in:**
- severe hepatic impairment Child-Pugh Class C
- for other contraindications see the prescribing guideline

**RECOMMENDED AS SECOND LINE**

- IF FIRST LINE THERAPY NOT AVAILABLE OR CONTRAINDICATED

**ALTERNATIVE**

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**CONSIDER**

- IF PATIENT IS SEROPOSITIVE AT TIME OF DIAGNOSIS (OR IF SEROSTATUS IS UNKNOWN)
References


4. Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial Montgomery, HughAbe, Wakana et al. The Lancet Respiratory Medicine, Published online June 7, 2022. DOI: https://doi.org/10.1016/S2213-2600(22)00180-1


## Version control

<table>
<thead>
<tr>
<th>Version</th>
<th>Amendments</th>
<th>Author/s</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>v 1-0</td>
<td>New document</td>
<td>Andrew Henderson Tina Patterson Amy Legg</td>
<td>CTWG 08/02/2022</td>
</tr>
<tr>
<td>v 1-1</td>
<td>Approved for publication: Keith McNeil A/Deputy Director-General, CMO and CCIO Prevention Division</td>
<td>Andrew Henderson Tina Patterson Amy Legg</td>
<td>11/02/2022</td>
</tr>
</tbody>
</table>
| v 1-2   | Addition of new sections:  
1.0 Classification of severity  
2.0 Treatment principles  
3.0 Overview of therapeutics for mild-moderate disease, including a statement on PBS listing of molnupiravir  
Amendments to existing content:  
s5.1 – addition of recommendation that patient self-administered RATs should be repeated by a healthcare worker.  
s5.3 and table 3 – Vaccination status and eligibility updated to reflect revised ATAGI definitions  
Table 5:  
• removal of the asthma biologics: benralizumab, mepolizumab, omalizumab and dupilumab and other anti-IL-17, anti-IL-23, anti-IL-6, anti-integrins, anti-TNF and checkpoint inhibitors, these agents are not anticipated to reduce the response to COVID-19 vaccination  
• Removal of hydroxychloroquine and addition of leflunomide to align with ATAGI definition of severe immunocompromise.  
• Nirmatrelvir plus ritonavir given preference provided no contraindications exist. Sotrovimab restricted to priority groups, in response to supply constraints. Remdesivir moved to first line therapy provided logistical challenge of three days IV therapy can be overcome. | Andrew Henderson Tina Patterson Amy Legg | |
<p>| v 1-2   | Content endorsed by COVID-19 Therapeutics Working Group | CTWG | 29/03/2022 |
| v 1-2   | Approved for publication: Keith McNeil A/Deputy Director-General, CMO and CCIO Prevention Division | | 31/03/2022 |
| v 1-3   | Updated vaccination status eligibility, fixed formatting based on feedback | Tina Patterson Amy Legg | 11/4/2020 |</p>
<table>
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<tr>
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<th>Approved</th>
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</table>
| V1-3    | Approved for publication: Keith McNeil  
A/Deputy Director-General, CMO and CCIO Prevention Division | | 17/04/2022 |
| V1-4    | Updated with tixagevimab and cilgavimab, eligibility for oral antiviral therapy amended from national taskforce criteria to PBS criteria | Andrew Henderson | |
| V1-4    | Approved for publication: Keith McNeil  
A/Deputy Director-General, CMO and CCIO Prevention Division | | 28/06/2022 |
| V1.5    | Updated molnupiravir and nirmatrelvir/ritonavir to align with PBS age and risk criteria  
Updated advice on nirmatrelvir/ritonavir in renal impairment  
Updated to include guidance for unvaccinated patients < 50 with risk factors  
Added information regarding sotrovimab application to TGA for increased dose (1000mg)  
Removed information on priority dosing for sotrovimab | Ashlea McCarron  
Andrew Henderson  
Panteha Voussoughi | 27/07/2022 |
| V1.5    | Approved for publication: Keith McNeil  
A/Deputy Director-General, CMO and CCIO Prevention Division | | 27/07/2022 |