Molnupiravir prescribing guideline

Published by the State of Queensland (Queensland Health), February 2022
This version published: June 2022

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1. Purpose

This guideline has been developed by the Queensland Health COVID-19 Therapeutics Working Group to provide clinicians with information and guidance around the appropriate prescribing and safe administration of molnupiravir (Lagevrio®) in patients diagnosed with COVID-19, and to ensure equity of access to new COVID-19 therapeutics. This guideline requires endorsement by local Drugs and Therapeutics Committees or equivalent prior to implementation.

2. Background

This guideline and procedure are based on the findings of the MOVe-OUT trial and recommendations of the National COVID-19 Clinical Evidence Taskforce (NCCET) and the NIH (US) and NICE (UK) guidelines. This document will be updated frequently as new evidence is made available.

2.1 Regulatory status

Molnupiravir has been granted provisional approval by the Therapeutic Goods Administration (TGA) for the treatment of adults with COVID-19 who do not require initiation of oxygen due to COVID-19 and who are at increased risk for hospitalisation or death.\(^1\)

Approval has been made based on limited data. More comprehensive evidence is required to be submitted prior to full registration. The product is subject to additional monitoring in Australia.

2.2 Mechanism of action

Molnupiravir is an oral pro-drug that is hydrolysed to the ribonucleoside analogue, beta-D-N4-hydroxycytidine (NHC), prior to reaching the systemic circulation. NHC distributes into cells where it is phosphorylated and incorporated into the viral RNA by viral RNA-polymerases. It subsequently misdirects the viral polymerase to incorporate either guanosine or adenosine during viral replications, leading to an accumulation of deleterious errors resulting in viral mutations and lethal mutagenesis. This mechanism of action is known as viral error catastrophe.\(^1,2\)

2.3 Efficacy

The data supporting molnupiravir is primarily based on the results of the MOVe-OUT trial. MOVe-OUT was a multinational, randomised, Phase 3 trial that compared molnupiravir 800 mg orally every 12 hours for 5 days to placebo. Study participants were non-hospitalised, Molnupiravir prescribing guideline – Department of Health v3 Published 28/06/2022
unvaccinated adults with mild-to-moderate, laboratory confirmed COVID-19 with onset of
signs or symptoms no more than 5 days earlier, and at least one risk factor for severe
disease: age > 60, active cancer, chronic kidney disease, chronic obstructive pulmonary
disease, obesity (BMI ≥ 30), serious heart conditions (heart failure, coronary heart disease,
or cardiomyopathies); or diabetes mellitus. Key exclusion criteria were an anticipated need
for hospitalisation for COVID-19 in the next 48 hours, dialysis or eGFR < 30 ml/min/1.73m²,
severe neutropenia (absolute neutrophil count < 500/mL), platelet count < 100,000/µL and
SARS-CoV-2 vaccination.3

In the final analysis of 1,433 participants, the primary composite outcome of death or all-
cause hospitalisation at day 29 had occurred in 48/709 (6.8%) participants in the treatment
arm and in 68/699 (9.7%) participants in the placebo arm. (30% relative risk reduction; -3.0%
adjusted difference; 95% CI, -5.9% to .01%; P = 0.0218). There was 1 death in the
molnupiravir arm and 9 deaths in the placebo arm.3

While efficacy against the Omicron variant is unknown, molnupiravir is expected to retain
activity.4

3. Prescription and governance

Molnupiravir has a restricted listing on the Queensland Health Medicines Formulary (List of
Approved Medicines):

For use as per the PBS indications

OR

For the treatment of COVID-19 in accordance with recommendations in the Statewide COVID-19
Treatment Guidelines and Molnupiravir prescribing guideline. Available at:
clinicians/clinical-guidelines

Individual governance of molnupiravir prescribing should be managed by a lead clinician in
each Hospital and Health Service.

Molnupiravir was listed on the Pharmaceutical Benefits Scheme (PBS) on March 1st, 2022,
with a streamlined authority for the treatment of SARS-CoV-2 infection. The PBS prescribing
criteria can be accessed via the PBS website.

3.1 Authorised prescribers

Hospital based prescribers (i.e., whose patients will access molnupiravir from the National
Medical Stockpile - via hospital pharmacies) no longer need to complete a Request to
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Access Form for each patient, confirming patient suitability and consent to treatment, provided molnupiravir is prescribed according to the COVID-19 Treatment Guidelines for mild to moderate disease (Adults).

3.2 Patient consent

There are no additional requirements for consent to administer molnupiravir than is usual practice for any other TGA registered pharmaceutical. Clinicians should discuss the risks and benefits of treatment with the patient and/or their carer and document that this has been done in the patient record. A molnupiravir Patient Information leaflet has been developed to assist with this and should be provided to the patient. Some clinicians may wish to obtain formal written consent and a generic COVID-19 Therapeutics consent form has been developed for this purpose. Consent forms and Patient Information are available online.

4. Access and supply

Access to molnupiravir is regulated by the National Medical Stockpile. Usage will be reviewed State-wide. While the PBS criteria are utilised for prescribing eligibility, supply of National Medical Stockpile medicines via public hospitals should occur as per usual arrangements.

5. Clinical criteria for treatment

There have been no head-to-head trials comparing molnupiravir with other treatment options, however, molnupiravir may have a lower level of efficacy and is only recommended when other more efficacious treatments such as nirmatrelvir plus ritonavir is not suitable or not available. Refer to the COVID-19 Treatment Guidelines for mild to moderate disease (Adult) for specific information.
5.1 Indications

Treatment of mild to moderate disease is based on PBS criteria for oral antiviral therapy.

Treatment criteria:

Non-hospitalised* patients with
- SARS-CoV-2 infection confirmed by either
  - Polymerase chain reaction (PCR) testing OR
  - 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** (Age > 65 or age > 50 if the patient identifies as Aboriginal or Torres Strait Islander and at least 2 of the following):
     - The patient has received less than 2 doses of SARS-CoV-2 vaccine
     - The patient is aged 75 years or over
     - The patient is in residential aged care or residential disability care
     - Neurological conditions, including stroke and dementia
     - Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis
     - Congestive heart failure (NYHA Class II or greater)
     - 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. **Patient with moderate to severe immunosuppression** defined as:
     - Any primary or acquired immunodeficiency including:
       - Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders

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- Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months),
- Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency
  - 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 (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 (more than 0.4mg/kg/week), leflunomide, azathioprine (at least 3mg/kg/day), 6-mercaptopurine (at least 1.5mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus)
  - Any significantly immunocompromising condition(s) where, in the last 12 months the patient has received rituximab,
  - Others with 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

*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.

Patients who identify as Aboriginal or Torres Strait Islander and who are aged over 35 but less than 50, and who are not up to date with vaccination with additional risk factors for severe COVID-19 infection (table 3), may be eligible for COVID-19 antivirals through the national stockpile scheme. Patients who meet this criteria will need to be managed through Hospital and Health Service Virtual Care Models or through Aboriginal community-control health services (ACCHS)

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NB. Molnupiravir is category D in pregnancy – in women of childbearing potential, the possibility of pregnancy and the need for a pregnancy test prior to commencing treatment should be considered. Sexually active women of childbearing potential must be counselled to use a reliable method of contraception or abstain from sex during and for four days after treatment.

5.2 Contraindications

Use is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. List of excipients: croscarmellose sodium, hyprolose magnesium stearate, microcrystalline cellulose, hypromellose. Capsule shell: iron oxide red, titanium dioxide, White ink: tert-butyl alcohol, ethanol absolute, isopropyl alcohol, potassium hydroxide, propylene glycol, shellac, titanium dioxide

5.3 Fertility, Pregnancy and Breastfeeding

Molnupiravir is TGA category D in pregnancy. Based on animal reproductive studies demonstrating embryofetal lethality and teratogenic effects at high doses, molnupiravir may cause foetal harm when administered to pregnant women. The manufacturer recommends that sexually active women of childbearing potential use effective contraception during and for four days after treatment with molnupiravir.1

It is unknown whether molnupiravir or any of the components of molnupiravir are present in human milk, affect human milk production, or affect the breastfed infant. Based on the potential for adverse reactions in the infant, the manufacturer advises breastfeeding is not recommended during treatment and for four days after the last dose of molnupiravir.1

There is no data on whether molnupiravir affects sperm. It is recommended that men who are sexually active with a partner of childbearing potential use effective contraception during and for three months after treatment with molnupiravir.1

5.4 Use in children

Safety and efficacy of molnupiravir has not been established in patients less than 18 years of age. However, bone and cartilage toxicity was observed at high doses in studies of rapidly growing rats over a 3-month period.1 The FDA emergency use authorisation of molnupiravir does not extend to children under the age of 18 due to concern it may affect bone and cartilage growth.5
5.5 Drug interactions

No formal drug-drug interaction studies have been undertaken with molnupiravir. Based on in-vitro studies, neither molnupiravir nor its active metabolite NHC are substrates of major drug metabolising enzymes or transporters. Therefore, the potential for molnupiravir or NHC to interact with concomitant medications is considered unlikely.¹

6. Prescribing and administration

6.1 Dose and duration

800 mg (4 x 200 mg capsules) orally TWICE daily for FIVE days.

Molnupiravir can be taken with or without food.

There are no dose adjustments required in elderly patients or those with renal or hepatic impairment.

6.1.2 Administration via enteral feeding tubes

There are limited data on the pharmacokinetics of molnupiravir following administration via enteral feeding tubes. Five participants enrolled in the phase 2 clinical study received at least one dose via nasogastric (NG) or orogastric (OG) tube. Concentrations from samples taken following oral administration were observed to fall within the same range as concentrations following administration via NG/OG tube, suggesting no difference in pharmacokinetics.⁶

Dose preparation:⁷

1. Open FOUR capsules and disperse contents in 40 mL of sterile water, mix or stir for 3 minutes.
2. Transfer the mixture to an enteral syringe.
3. Flush the tube with 5 mL of water. Shake the enteral syringe for one minute then give via the tube. Flush the tube twice with 5 mL of water.
4. Dose should be given within 2 hours of preparing the dispersion.
Further information on preparation of an oral solution can be found at Oral antiviral treatment for COVID-19 (nps.org.au). In patients unable to tolerate thin fluids, the capsule may be opened and mixed with a spoonful of yoghurt or apple puree. Absorption is not expected to be impacted by mixing the contents of the capsules with soft food.

6.2 Presentation, storage, and stability

Molnupiravir is supplied as an opaque orange capsule imprinted with a corporate logo and “82” in white ink. Each capsule contains 200 mg of molnupiravir.

Molnupiravir capsules are packaged in a bottle containing 40 capsules, and should be stored in the original bottle below 30°C.

6.3 Adverse effects and reporting

The safety of molnupiravir was evaluated based on an analysis of the Phase 3, double-blind MOVe-OUT trial in which 1,411 non-hospitalised subjects with COVID-19 were randomised to treatment with molnupiravir (n=710) or placebo (n=701) for up to 5 days and followed through Day 29. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion or discontinuation.

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving molnupiravir and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% of subjects receiving placebo. None were considered drug-related by the investigator and most were COVID-19 related.

The most common adverse reactions reported in the molnupiravir treatment group were:

- diarrhoea
- nausea
- dizziness

It may be difficult to distinguish between adverse effects of molnupiravir and signs and symptoms of COVID-19. However, because molnupiravir is a provisionally approved product with no post-marketing data, all possible and confirmed adverse events must be reported. These should be notified to the TGA Reporting adverse events | Therapeutic Goods Administration (TGA) and reported via Riskman.
7. Vaccination after molnupiravir

Suitability for ongoing vaccination is related to the patient’s recovery from COVID-19 and is not influenced by receipt of molnupiravir.

8. Compliance and evaluation

Regular prescribing reports will be provided through interrogation of iPharmacy, ieMR and CHARM programs. Reports will be made available to Medication and Pharmacy Planning Response Group (MPPRG).
9. References


## 11. Version Control

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<td>Approved: Feb 2022</td>
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<td>CTWG</td>
<td>08/02/2022</td>
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<td>Added significant bronchiectasis to risk factors in table. Removed 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 Updated immunosuppressive medications to remove hydroxychloroquine and add leflunomide in line with ATAGI definitions for severe immunosuppression Added information on PBS listing Updated vaccination status eligibility (table 1)</td>
<td>Tina Patterson,Amy Legg</td>
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| v3-0    | Inclusion of reference to the PBS prescribing criteria and access arrangements for public hospitals  
Removed requirement to complete RTA form as no longer required  
Aligned criteria for therapy to the PBS and linked to the COVID-19 Treatment Guidelines for mild to moderate therapy (Adult)  
Removed monitoring of treatment outcomes as no longer reported to National Medical Stockpile Taskforce  
Removed Appendix 1 and 2 Priority Criteria and Summary of key difference: PBS vs QLD health eligibility criteria as eligibility now as per the COVID-19 Treatment Guidelines for mild to moderate therapy (Adult) | Ashlea McCarron             |            |
| v 3-0   | Approved for publication: Keith McNeil  
A/Deputy Director-General, CMO and CCIO Prevention Division                                                                                                                                                            |                           | 28/06/2022 |