Molnupiravir (Lagevrio®) has been provisionally approved by the Therapeutic Goods Administration for use in Australia 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. This decision has been made on the basis of the analysis of efficacy and safety data from a Phase 3 trial. Continued approval of this indication depends on additional data from ongoing clinical trials and post-market assessment. Molnupiravir (Lagevrio®) is not intended to be used as a substitute for vaccination against COVID-19.

The National COVID-19 Clinical Evidence Taskforce provides consensus recommendations (current as at date of publishing) for use of molnupiravir oral antiviral therapy within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are unvaccinated and who have one or more risk factors for disease progression, where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available
- are immunosuppressed or not immunocompetent, regardless of vaccination status, where other treatments are not suitable or available
- have received one or two doses of vaccine and who are at high risk of severe disease on the basis of age and multiple risk factors, where other treatments are not suitable or available.

Efficacy and safety information for molnupiravir are based on data from 1,433 randomised subjects in the Phase 3 MOVe-OUT trial. MOVe-OUT is a randomised, placebo-controlled, double-blind clinical trial studying molnupiravir for the treatment of non-hospitalised patients with mild to moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalisation. The study included symptomatic patients who were not vaccinated against COVID-19 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomisation. Subjects were randomised 1:1 to receive 800 mg of molnupiravir or placebo orally twice daily for 5 days.

This medication is regulated by the National Medical Stockpile (NMS). Access to stock requires completion of a WA Emergency COVID-19 Treatment Approval for Molnupiravir (Lagevrio®) Form and confirmation by the prescriber that the patient fulfils required criteria.

Supply of COVID-19 therapeutics via the NMS is uncertain and availability is expected to fluctuate with demand and constraints in the supply chain. To ensure equity of access and conserve molnupiravir (Lagevrio®) therapy for those patients at the highest risk of disease progression, a tiered access criterion is in place to allocate stock taking into account current supply.

This guideline should be used in conjunction with the molnupiravir (Lagevrio®) resources available:

- WA Emergency COVID-19 Treatment Approval for Molnupiravir (Lagevrio®) Form
- Patient Consent Form and further information regarding consent, and
- Lagevrio® Patient Information Leaflet.
- WA Health Molnupiravir Patient Information Leaflet
FOR TREATMENT OF COVID-19

Drug Class\textsuperscript{1,2}: Molnupiravir is an antiviral medication that works via a mechanism of action known as viral error catastrophe. It is a prodrug that is metabolised to the ribonucleoside analogue n-hydroxycytidine (NHC). NHC distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation into viral RNA by the viral RNA polymerase results in an accumulation of errors in the viral genome leading to inhibition of replication.

Clinical Criteria\textsuperscript{2}: Within the patient population for which molnupiravir is recommended for use, decisions about the appropriateness of treatment with molnupiravir should be based on the patient’s individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

Unvaccinated patients
As per the National COVID-19 Clinical Evidence Taskforce Guidelines, adults are eligible for treatment with molnupiravir if:

- they are unvaccinated against COVID-19; \textbf{AND}
- they are within five (5) days of symptom onset; \textbf{AND}
- they have mild to moderate COVID-19 disease (i.e. do not require oxygen); \textbf{AND}
- they have \textbf{one or more of the risk factors} for disease progression (below); \textbf{AND}
- other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

Risk factors:
Based on the inclusion criteria for the MOVe-OUT trial, risk factors for disease progression include the following:

- Age \geq 60 years
- Obesity (BMI \geq 30kg/m\textsuperscript{2})
- Chronic kidney disease (i.e. eGFR <60 mL/min/1.73m\textsuperscript{2} by MDRD), excluding patients on dialysis
- Serious heart conditions such as heart failure, coronary artery disease or cardiomyopathies
- Chronic obstructive pulmonary disease
- Active cancer (excluding minor cancers not associated with immunosuppression, e.g. basal cell carcinomas)
- Immunocompromised state following solid organ transplant
- Sickle cell disease
- Diabetes mellitus

Available research does not currently provide enough evidence to determine the benefits of molnupiravir in specific subgroups of patients. In the absence of definitive evidence, the
Taskforce has arrived at a consensus recommendation based on their clinical expertise to guide clinical decisions about which patients are most likely to benefit from molnupiravir.

There is no evidence evaluating the effectiveness of molnupiravir in partially or fully vaccinated patients. Given this, and the lower risk of deterioration in these patients, it is unlikely that molnupiravir will have a significant treatment benefit in patients who have received three doses of vaccine, unless the patient is immunosuppressed.

There is limited evidence on the effectiveness of molnupiravir in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that molnupiravir will be beneficial for immunosuppressed patients.

**Immunosuppressed patients or patients at high risk of severe disease**

Accordingly, in addition to at-risk unvaccinated adults, molnupiravir may also be considered for use within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunosuppressed or not immunocompetent regardless of vaccination status; or
- have received one or two doses of vaccine and who are at high risk of severe disease on the basis of age and multiple risk factors (see above);

**AND** where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

Severe immunocompromising conditions include:

- Patients who are within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving Bruton tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic stem cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid-organ transplant (other than lung transplant) or haematopoietic stem cell transplant
- Solid-organ transplant recipients with recent treatment for acute rejection with T or B cell depleting agents
- Patients with certain primary immunodeficiencies
  - PIDS affecting cellular and humoral immunity (severe and other combined immunodeficiencies [https://doi.org/10.1007/s10875-019-00737-x ])
  - PIDS with profoundly decreased or absent B cell number or function
  - PIDS with impaired interferon responses
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm³
- Patients on any of the following agents not already listed
  - Anti-CD20 antibodies rituximab, obinutuzumab, ocrelizumab, ofatumumab
  - BTK inhibitors ibrutinib, acalabrutinib, zanubrutinib
  - Sphingosine 1-phosphate receptor modulators fingolimod, siponimod
  - Anti-CD52 antibodies alemtuzumab
  - Anti-complement antibodies eculizumab
  - Anti-thymocyte globulin

Please refer to ATAGI Recommendations on the use of a 3rd primary dose of COVID-19 vaccine in individuals who are severely immunocompromised.
Contraindications:\(^1\):
Hypersensitivity to the active substance or to any of the excipients (Croscarmellose sodium, Ethanol absolute, Hyprolose, Hypromellose, Iron oxide red, Isopropyl alcohol, Magnesium stearate, Microcrystalline cellulose, Potassium hydroxide, Propylene glycol, Shellac, Strong ammonia solution, Tert-butyl alcohol, Titanium dioxide).

Special Warnings and Precautions for Use:\(^1\):
- **Paediatric patients:** The safety and efficacy of molnupiravir has not been established in patients less than 18 years of age, therefore use in paediatric patients is not recommended. Molnupiravir may affect bone and cartilage, consisting of an increase in the thickness of physeal and epiphyseal growth cartilage with decreases in trabecular bone.
- **Use in the elderly:** In the MOVe-OUT trial, there was no difference in safety and tolerability between patients >65 years of age and younger patients who were treated with molnupiravir. No dose adjustment is recommended based on age.
- **Use in pregnancy (Category D):** The use of molnupiravir is not recommended during pregnancy. Women of childbearing potential should be advised to use effective contraception for the duration of treatment and for at least four (4) days after the last dose of molnupiravir. Based on animal data, molnupiravir may cause fetal harm, and there are no available data on the on the use of molnupiravir in pregnant women to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
- **Fertility** - There is no data available on whether molnupiravir affects sperm. It is recommended that men who are sexually active with a partner of childbearing potential use an adequate form of contraception during and for three (3) months after treatment with molnupiravir.
- **Use in lactation:** It is unknown whether molnupiravir or any of the components of molnupiravir are present in human milk, affect human milk production, or have effect on the breastfed infant. Breastfeeding is not recommended during treatment and for four (4) days after the last dose of molnupiravir.

Drug Interactions:\(^1\):
No drug interactions have been identified based on the limited data currently available.

Clinical drug-drug interaction trials of molnupiravir with concomitant medications have not been conducted. Neither molnupiravir nor NHC are inhibitors or inducers of major drug metabolising enzymes or transporters. Therefore, the potential for molnupiravir or NHC to interact with concomitant medications is considered unlikely.

The University of Liverpool COVID-19 Drug Interactions checker\(^3\) can be used to check for specific interactions between molnupiravir and other medications/medication classes as further information becomes available through clinical trials and ongoing assessments.
**Presentation and Storage**: 

Lagevrio® is available as a ‘Swedish Orange’ opaque capsule with “82” printed with white ink. Each capsule contains 200mg of molnupiravir. Lagevrio® should be stored below 30°C in the original bottle, away from heat, light and moisture.

**Dose**: 

The recommended dose of Lagevrio® is 800 mg (i.e. four 200mg capsules) taken orally every 12 hours for 5 days. Lagevrio® capsules may be taken with or without food and should be swallowed whole (i.e. not opened, broken or crushed). The safety and efficacy of molnupiravir when administered for more than 5 days has not been established. If the patient misses a dose of Lagevrio® 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.

In women of childbearing potential, healthcare providers should discuss the chance that they may be pregnant and consider the need for a pregnancy test before commencing treatment. No dosage adjustment is required in patients with renal impairment, and no dosage adjustment is recommended in patients with hepatic impairment.

**Adverse Effects**: 

The most common adverse reactions in the molnupiravir treatment group in the MOVE-OUT trial were diarrhoea (2%), nausea (1%) and dizziness (1%), all of which were Grade 1 (mild) or Grade 2 (moderate). While serious adverse events occurred in 7% of patients receiving molnupiravir, none were considered drug-related by the investigator and most were COVID-19 related.

Refer to the product information for a complete list of possible adverse effects.

As molnupiravir is a provisionally approved medicine which has no relevant post-marketing data, 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.

**Reporting**: 

As molnupiravir is a provisionally approved medicine and only available through the National Medical Stockpile prescribers must complete and submit a WA Emergency COVID-19 Treatment Approval for Molnupiravir (Lagevrio®) Form, for approval for each patient they intend to treat.

This will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines use. The prescribing clinician and any healthcare professional administering molnupiravir is responsible for reporting medication errors related to molnupiravir treatment.
Please note: This does not apply to Residential Aged Care Facilities and Aboriginal Community Controlled Health Organisations (ACCHOs) that have received stock directly from the Commonwealth. It is expected that stock management under these circumstances will be managed as per the Authorisation to supply or administer a poison COVID-19 Treatment – National Medical Stockpile and local processes.

Lagevrio® is subject to additional monitoring in Australia to allow quick identification of new safety information. Healthcare professionals should report any suspected adverse events to the TGA at http://www.tga.gov.au/reporting-problems.

Any clinical incidents related to treatment with molnupiravir that occur within the WA public health system should also be notified into the Datix CIMS and investigated appropriately.
References:
This guidance is correct at the time of publishing. However, as it is subject to updates, please use the hyperlinks to confirm the information is accurate.

WA guidance may be amended as additional National guidance is finalised and/or further information becomes available.