



DRUG GUIDELINE - MOLNUPIRAVIR (LAGEVRIO®)

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.

As per the [PBS Listing](#), adults (18 years and over) are eligible for treatment with molnupiravir if the patient:

- has received a positive PCR or RAT result (RAT must be verified by medical practitioner); AND
- has at least one sign or symptom* attributable to mild to moderate COVID-19 (i.e. do not require oxygen) and do not require hospitalization at the time of prescribing; AND
- is within five (5)* days of symptom onset; AND
- is aged 50 years or over (ATSI 30 years and over) and at high risk OR 'moderately or severely' immunocompromised.

is aged 70 years or over

*As of 11th July 2022, asymptomatic patients aged 70 years or over are eligible for treatment after a positive test. 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.

This medication is also available via the National Medical Stockpile (NMS) for cases where a prescriber considers treatment is clinically indicated but the patient is not eligible under the PBS. Access to stock through this mechanism 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.

National Medical Stockpile stock of molnupiravir must NOT be used to dispense a PBS prescription.

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^{1,3}:

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 Criteria²:

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 and on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

As per the [PBS eligibility criteria](#) from 11 July 2022, adults (18 years and over) are eligible for treatment with molnupiravir if the patient:

- has received a positive PCR or RAT result (RAT must be verified by medical practitioner); AND
- has at least one sign or symptom* attributable to mild to moderate COVID-19 (i.e. do not require oxygen) and do not require hospitalization at the time of prescribing; AND
- is within five (5)* days of symptom onset; AND
- is aged 70 years or older*
- is aged 50 years of age or older, with two additional risk factors for developing severe disease
- is aged 30 years of age or older, identifying as Aboriginal or Torres Strait Islander, with two additional risk factors for developing severe disease; and
- is aged 18 years of age or older, with moderate to severe immunocompromise

*As of 11th July 2022, asymptomatic patients aged 70 years or over are eligible for treatment after a positive test.

The following is a list of risk factors (conditions) contributing to the PBS definition of high risk for development of severe disease.

- The patient is in residential aged care,
- The patient has disability with multiple comorbidities and/or frailty
- Neurological conditions, including stroke and dementia and demyelinating conditions e.g. multiple sclerosis, Guillain-Barre Syndrome
- Respiratory compromise, including COPD, moderate or severe asthma (required inhaled steroids), and bronchiectasis, or caused by neurological or musculoskeletal disease,
- Heart failure, coronary artery disease, cardiomyopathies
- 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, or
- 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.

For the purpose of PBS eligibility, “moderately to severely immunocompromise” patients are those with:

1. Any primary or acquired immunodeficiency including:
 - a) Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cell disorders,
 - b) Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months),
 - c) Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency OR
2. Any significantly immunocompromising condition(s) where, in the last 3 months the patient has received:
 - a) Chemotherapy or whole-body radiotherapy,
 - b) 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,
 - c) 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),
 - d) 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) OR
3. Any significantly immunocompromising condition(s) where, in the last 12 months the patient has received rituximab, OR
4. Others with very high-risk conditions including Down Syndrome, cerebral palsy, congenital heart disease, thalassemia, sickle cell disease and other haemoglobinopathies OR
5. People with disability with multiple comorbidities and/or frailty

Contraindications¹:

Hypersensitivity to the active substance or to any of the excipients (Croscarmellose sodium, Ethanol absolute, Hypromellose, 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 Use¹:

- **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 physal and epiphysal 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 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 Interactions¹:

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 checker³ 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 Storage¹:

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^{1,2}:

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 Effects¹:

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.

Appendix 1: Preparing an oral solution of molnupiravir (Lagevrio)⁵

While the recommendation is to swallow molnupiravir capsules, if alternative treatments are not available or not suitable, follow the manufacturers advice to prepare an oral solution.

Dose Preparation

1. Open 4 capsules and transfer contents into a cup or syringe. Discard empty capsules per local procedures.
2. Add approximately 40 mL of water to the cup or syringe.
3. Mix/stir the capsule contents and water for 3 minutes:
 - Note that insoluble capsule contents may not dissolve completely.
 - Reconstituted solutions prepared according to directions may have visible undissolved particulates and are acceptable for oral administration.
4. Ensure that administration occurs as soon as possible after the preparation, and no later than 2 hours after the preparation.

Administration procedure:

1. Oral dose should be administered by staff wearing personal protective equipment required per local standards.
2. Stir the solution for 1 minute prior to administration to re-mix the suspension.
3. Follow local procedures for disposal of hazardous and/or biohazardous waste.
4. Wash hands following dose administration.

Specific nasogastric/orogastric (NG/OG) tube guidance:

1. Shake to mix the administration syringe for 1 minute prior to administration to re-mix the suspension.
2. Flush NG/OG tube with five mL of water prior to administration.
3. Administer entire volume from the administration syringe.
4. Flush tube with 5 mL of water twice (10 mL in total) after administration of the solution.

Note that:

- administration of molnupiravir via an oral solution has not been evaluated in a clinical trial and is regarded as off-label. If using, document the decision in the patient record and obtain consent from the patient or their designated decision-maker
- molnupiravir is soluble in water and it is recommended to mix capsule contents with water before administration.
- there is limited experience with administration of oral solution via NG/OG tube.
- anyone preparing the solution should consider the risks of exposure (e.g., see Lagevrio Product Information: Section 4.6 Fertility, Pregnancy and Lactation).

References:

1. Australian Product Information - Lagevrio® (molnupiravir). TGA; 2022.
<https://www.tga.gov.au/sites/default/files/lagevrio-pi.pdf> Accessed 8 February 2022
2. PBS Listing for molnupiravir - <https://www.pbs.gov.au/medicine/item/12910L> (Access 17 March 2022)
3. National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. <https://covid19evidence.net.au/#living-guidelines> . Accessed 17 March 2022
4. University of Liverpool. COVID-19 Drug Interactions checker.
<https://www.covid19-druginteractions.org/checker>
5. National Prescribing Service (NPS) MedicineWise – Molnupiravir
<https://www.nps.org.au/radar/articles/molnupiravir-lagevrio-for-mild-to-moderate-covid-19> (Accessed 17 March 2022).
6. Lagevrio® (molnupiravir) PBS Factsheet – Updated July 2022. factsheet-lagevrio-july-2022.pdf (pbs.gov.au) (Accessed 11 July 2022)
<https://www.pbs.gov.au/news/2022/04/files/Factsheet%20Paxlovid.pdf>

Version Control

Version	Date	Comments
1.0	21/02/2022	Consultation with COVID-19 Treatment EAG
1.1	24/02/2022	Endorsed by COVID-19 Treatment EAG
2.0	17/03/2022	Updated with PBS listing information
3.0	26/07/2022	Updated with expanded PBS listing information

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.

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