Government of **Western Australia**
Department of **Health**

May 2023

Molnupiravir (Lagevrio®)

What Prescribers and Pharmacists Need to Know

Why is molnupiravir used to treat COVID-19?

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.

What is the benefit of molnupiravir for COVID-19?

The Pharmaceutical Benefits Advisory Committee (PBAC) are satisfied that, for some patients, molnupiravir is likely to be more efficacious than the current standard of care in reducing the risk of developing severe disease leading to hospital admission. The PBAC acknowledged that most antivirals for COVID-19 have only been evaluated in unvaccinated people.

Current recommendations are for people who are at higher risk of primary vaccine failure (such as people who are immunocompromised) or have high risk of disease progression.

- PBAC - Web Outcome Statement for Molnupiravir- February 2022

Based on preliminary results of the PANORAMIC trial, the National Clinical Evidence Taskforce have suggested that in people who are highly vaccinated that molnupiravir may not make a difference to the risk of hospitalisation, as their risk of hospitalisation is already low. The COVID-19 Treatment Expert Advisory Group reviewed evidence independently in the WA context along with the statement provided recently by Prof. Michael Kidd on the 9 Dec 2022, and recommend that molnupiravir may make a difference to the duration of a patient's symptoms and the patient's viral load and still has a place in therapy when Paxlovid® is contraindicated or otherwise unsuitable.

Who should receive molnupiravir?

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. Molnupiravir should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable.

It is recommended that the patient be provided with a molnupiravir patient information leaflet and that patient consent is obtained prior to commencing therapy.

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

- Has received a positive PCR or RAT result **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 hospitalisation at the time of prescribing; **AND**
- Is within five (5)* days of symptom onset; **AND**
- At least 18 years of age and 'moderately to severely immunocompromised', or
- Is aged 50 years or over with two risk factors, or
- Identify as Aboriginal and Torres Strait Islander, at least 30 years of age with one risk factor
- Had a past COVID-19 infection episode resulting in hospitalisation
- *Can be started after a positive test in asymptomatic patients 70 years and over

PBS risk factors include:

- 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,
- 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/m^2),
- 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.

Who should receive molnupiravir continued …

‘Moderately to severely immunocompromised’ 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 (at least 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 an anti-CD20 monoclonal antibody treatment, but criterion 2c above is not met; 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.

Molnupiravir dosing requirements for treatment of COVID-19

The recommended dose of molnupiravir is:

800 mg (4 x 200mg capsules) taken orally every 12 hours for 5 days.

Molnupiravir 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.

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 or hepatic impairment.

It is important for health professionals to minimise handling of the molnupiravir capsules, especially if pregnant. Use personal protective gloves when handling.

For patients with swallowing difficulties, consult ‘Don’t Rush to Crush’ or a Hospital Medicines Information Pharmacist for further information. Please note that anyone preparing the solution should consider the risks of exposure as per Product Information Section 4.6 Fertility, Pregnancy and Lactation.

What if a patient misses a dose?

If the patient misses a dose of molnupiravir within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule.

If a patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

What side effects should I be aware of?

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.

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.

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.

For further information:

Visit:

- Lagevrio Product Information (tga.gov.au)
- WA COVID-19 Information for health professionals - under Clinical Guidelines

Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

Excipients include: 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, and titanium dioxide.

What drug interactions should I consider before prescribing molnupiravir?

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.

Special Warnings and Precautions for Use:

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 effective form of contraception during treatment and 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.

Access to National Medical Stockpile Medicines

It is important to note that the mechanism for accessing molnupiravir through the National Medical Stockpile (NMS) will continue for cases where a prescriber considers treatment is clinically indicated but the patient is not eligible under the PBS.
Access of all NMS COVID-19 medications requires consultation and review by an Infectious Disease Physician for eligibility and approval. If approved, it will be dispensed by a WA public hospital which will arrange supply for collection by a support person or delivered to the patient.

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

IMPORTANT: National Medical Stockpile molnupiravir must not be dispensed as a PBS prescription.

Additional information may be found in the:

- Australian Product Information - Lagevrio® (molnupiravir). TGA; 2022. https://www.tga.gov.au/sites/default/files/lagevrio-pi.pdf
- PBS Listing for molnupiravir - https://www.pbs.gov.au/medicine/item/12910L
- National Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19.https://clinicalevidence.net.au/covid-19/#living-guidelines. Version 50.1 published 3 February 2022.
- University of Liverpool. COVID-19 Drug Interactions checker. https://www.covid19-druginteractions.org/checker
- Don’t rush to crush 4th Edition March 2022. Society of Hospital Pharmacy Australia.