Information and guidance for the health sector: oral therapeutic agents for treatment of COVID-19 in the community

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1.Introduction

Background

Nirmatrelvir with ritonavir (Paxlovid™) has been available for prescribing and dispensing since Tuesday 5 April.

Molnupiravir (Lagevrio®) has now arrived in Aotearoa and will be available to prescribe and dispense from Thursday 5th May 2022.

Pharmac has secured access to 60,000 courses of Paxlovid™ and 60,000 courses of molnupiravir for use in 2022.

The access criteria for oral COVID-19 antiviral medicines have been widened from 5 May 2022, enabling people with fewer co-morbidities to be eligible. In particular, Māori or Pacific Island people aged 65 and over who have not completed a full course of vaccination (as per the Ministry of Health definition) will not need any co-morbidities to be eligible for access to these medications.

Nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) are new to the market, and information about their prescribing and dispensing safety is important to consider. The use of nirmatrelvir with ritonavir (Paxlovid™) is further complicated by the significant number of clinically important drug-drug interactions.

For these reasons, pharmacists and prescribers are strongly encouraged to manage drug interactions and dose adjustments collaboratively and keep up to date with training opportunities, and drug information.

Indication

Nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) are oral antivirals used to treat COVID-19 in the viral replication phase of the infection.

Preliminary evidence suggests both oral antivirals are effective against the Omicron variant in reducing the development of serious illness and hospitalisation in those who are most at risk.

It should be noted that the COVID-19 vaccination booster dose is also very effective against reducing the rate of hospitalisation and should be prioritised for all people and especially for those with higher risk conditions.

Special considerations

An in-person consultation is not needed to prescribe nirmatrelvir with ritonavir (Paxlovid™) or molnupiravir (Lagevrio®). When assessing eligibility, shared decision making between primary care practitioner, patient, health providers and whānau is encouraged.

There is currently no privately funded supply for either of these medicines. Prescriptions for patients who do not meet access criteria will not be able to be dispensed unless an authorised prescriber has applied for a Named Patient Pharmaceutical Assessment (NPPA) for patients who have exceptional clinical circumstances and do not meet access criteria.

Place in Therapy

Available evidence demonstrates that nirmatrelvir with ritonavir (Paxlovid™) is more effective than molnupiravir (Lagevrio®) at reducing the risk of hospitalisation.[1,2] Therefore, nirmatrelvir with ritonavir (Paxlovid™) is the oral COVID-19 antiviral of choice unless it is contraindicated, otherwise unsuitable, or unavailable due to constrained stock.

The clinical trials for nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) were conducted prior to Omicron becoming the dominant variant, and the enrolled participants were unvaccinated adults.

The transferability of these findings to the current COVID-19 setting in Aotearoa is uncertain, due to our highly vaccinated population, and because Omicron is the dominant variant.

However, both nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) are expected to maintain activity against Omicron and still have a place in therapy for those most at risk of severe outcomes.

Nirmatrelvir with ritonavir (Paxlovid™)

Dosage

Paxlovid™ is a 5-day course of two medicines:

- a protease inhibitor **nirmatrelvir** (2 pink tablets twice daily) that blocks virus replication
- **ritonavir** (1 white tablet twice daily) which slows the metabolism of nirmatrelvir.

Treatment is recommended to be initiated as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

Dose adjustment of the nirmatrelvir component is necessary where there is renal impairment. No dose adjustment is required where there is mild or moderate hepatic impairment.

Contraindications include those with eGFR < 30 mL/minute, severe hepatic impairment, and pregnancy.

Interactions/precautions

Ritonavir is a potent inhibitor of several important CYP enzymes responsible for drug metabolism (e.g., CYP3A4, CYP2D6) and transporter proteins (e.g., P-glycoprotein) which leads to it having multiple significant drug interactions.

Depending on the severity of interaction and relative importance of the other drug, nirmatrelvir with ritonavir (Paxlovid™) may be contraindicated, or a dose adjustment may be required of either the nirmatrelvir component or some of the patient's usual medicines.

Careful consideration is necessary to weigh the potential benefits versus risks of temporarily halting regular medicines and treating the COVID-19 infection. It is recommended to discuss concerns with secondary care specialists if they are also prescribing for the patient.

Extra contraception precautions are recommended during and for a week after treatment, particularly when oral contraception is being used.

Molnupiravir (Lagevrio®)

Dosage

Molnupiravir (Lagevrio®) is formulated as 200 mg capsules. The dose is 800 mg (4 capsules) taken twice daily (every 12 hours) for 5 days.

Treatment is recommended to be initiated as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

No dose adjustment is required in patients with renal impairment, and no dose adjustment is recommended in patients with hepatic impairment.

Interactions/precautions

Neither molnupiravir (Lagevrio®) nor its active metabolite are inhibitors or inducers of major drug metabolizing enzymes or transporters. No drug interactions have been identified based on the limited available data.

Molnupiravir (Lagevrio®) should not be used during pregnancy. Although there are no human pregnancy data, animal studies have demonstrated foetal developmental abnormalities with molnupiravir (Lagevrio®) exposure.

Effective contraception is recommended in people of childbearing potential for the duration of treatment and for 4 days after the last dose of molnupiravir (Lagevrio®). The manufacturer also recommends that males who have partners of childbearing potential use reliable contraception during and for 3 months after treatment.

Breastfeeding is not recommended during treatment and for 4 days after the last dose of molnupiravir (Lagevrio®).

2. Key Resources

- Pharmac Access Criteria
- Clinical guidance on Health Pathways Case Management in Adults pathways
- The New Zealand Formulary (NZF) drug monographs for nirmatrelvir with ritonavir and molnupiravir
- He Ako Hiringa have a resource to guide review of drug interactions with nirmatrelvir with ritonavir (Paxlovid™) and are preparing a resource to guide the use of molnupiravir (Lagevrio®) that will be published later in May
- Nirmatrelvir with ritonavir (Paxlovid™) datasheet and molnupiravir (Lagevrio®) datasheet
- Health Navigator have created plain-language consumer information leaflets for nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®)

A recording of the HealthPathways webinar that focused on nirmatrelvir with ritonavir (Paxlovid™), can be found here.

3. Responsibilities

Distribution

- Nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) are being distributed by the wholesaler to participating pharmacies. Participating pharmacies have been determined at a local level based on high need population demographics. A list of each regions' participating pharmacies can be found on HealthPathways.

Prescribing

- Eligible patients will be identified and confirmed as meeting access criteria on the initial clinical assessment of the COVID-19 case.
- The prescriber has the responsibility for the clinical review, ensuring the dose is appropriate for the renal function, that potential drug interactions are being managed appropriately, and that there are no other contraindications. Patient perspectives need to be taken into account and clinical judgement is to be applied, and important considerations documented.
- The prescription will be sent directly to the local participating pharmacy.

Dispensing

- The participating pharmacy will check that the most appropriate oral COVID-19 antiviral is being prescribed, that the patient is aware of the drug interactions with nirmatrelvir with ritonavir (Paxlovid™), and how to adjust their medicines if necessary. This may entail contacting the patient's usual pharmacy if the participating pharmacy is not the patient's usual pharmacy and collaboration with their general practice team. The pharmacy will dispense the medicine, provide advice to the patient, and organise delivery.

Monitoring

- The Ministry of Health and Pharmac will review supply and COVID-19 case data to inform stock management, and quality control processes.
- These medicines are new to the market, and information about their safety and effectiveness is limited. It is therefore important for pharmacists and prescribers to report any suspected adverse drug events to the Centre for Adverse Reactions Monitoring (CARM).

4. Process details

Prescriber

How will the COVID-19 cases who are at higher risk of hospitalisation be identified?

- A desktop risk assessment for COVID-19 cases will identify the COVID-19 cases that need an initial clinical assessment.
- The eligibility for treatment will be determined using clinical judgement, discretion and interpretation of the Pharmac access criteria. This assessment and the prescribing process are ideally both completed in the COVID-19 Care in Community initial clinical assessment consultation.
- Many practices will already be aware of several of their patients who are most vulnerable (for example, the severely immunosuppressed include those that were eligible for third primary dose of COVID-19 vaccination or those patients in geographically isolated communities). These people can be informed of the need to test urgently should they develop symptoms or become household contacts of a case.
- Cases that are not enrolled with a local general practice will be prioritised for a call from the Care Coordination Hub level to coordinate an initial clinical assessment. Information provided on the National Contact Tracing Solution (NCTS) self-assessment form will assist with prioritisation and allocation to clinical provider.

Checks and considerations when prescribing an oral COVID-19 antiviral therapeutic.

- Check whether the patient meets the Pharmac access criteria.
- Review suitability of the therapeutic, specifically any contraindications and whether the patient wants active intervention.
- Discuss the implications of treating with nirmatrelvir with ritonavir (Paxlovid™) with secondary care clinicians who may be co-prescribing higher-risk medicines for the patient (e.g., nephrologist or oncologist).
- Consider the advice needed for those secondary parties acting on behalf of the patient (for example, Māori health providers).
- Consider checking a pregnancy test in people of childbearing potential, and where appropriate check whether breastfeeding before prescribing.
- If prescribing nirmatrelvir with ritonavir (Paxlovid™):
    - Review renal function and consider dose adjustment if eGFR < 60 mL/minute.
    - Review potential drug interactions.
    - Manage any necessary dose adjustments of medicines. Communicate this clearly to the patient and document details in notes. The community pharmacist will also be undertaking a medicine review and will need to be able to contact you with any concerns.

How to prescribe an oral COVID-19 antiviral therapeutic:

1. **Document** key information on the prescription, including

    - endorsing that the person meets the access criteria,
    - date of symptom onset,
    - latest eGFR for nirmatrelvir with ritonavir (Paxlovid™) (if available),
    - prescriber's contact phone number.

    (The contact number provided to the pharmacist needs to support easy access for urgent queries regarding medicines management. Prescribers and practices are asked to prioritise calls from pharmacists due to the tight timelines involved in needing to get the prescription to the patient).

2. **Issue** the prescription and send electronically to the local participating pharmacy.

3. **Provide** written information or links to information on how to take the medicine.

What needs to happen next?

- Active case management will include regular review and management of clinical progress.
- Check for adverse effects and report these to CARM.
- Audit of prescriptions, including eligibility criteria and outcomes is encouraged.

Pharmacists

Who is the wholesaler?

Pharmac have contracted ProPharma as the community wholesaler for nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®).

What are participating pharmacies?

Due to limited stock, and to help ensure equitable access to oral COVID-19 medicines, specified participating pharmacies have been identified to deliver this service. These pharmacies have been identified locally and can be updated over time.

Only participating pharmacies can order and supply nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®).

How do I order stock of nirmatrelvir with ritonavir (Paxlovid™) or molnupiravir (Lagevrio®)?

Stock can be ordered from ProPharma using standard processes.

If the supply of nirmatrelvir with ritonavir (Paxlovid™) or molnupiravir (Lagevrio®) becomes constrained, restrictions may be placed on ordering. Your DHB pharmacy portfolio manager will be able to offer guidance if this situation occurs.

What do I need to do when reviewing a script for nirmatrelvir with ritonavir (Paxlovid™) or molnupiravir (Lagevrio®)?

Every prescription must be reviewed for completeness and appropriateness. Unless contraindicated, patients requiring a COVID-19 oral antiviral should usually be offered Paxlovid™ in the first instance because it is a more effective treatment option.

All prescriptions must be endorsed that the patient meets Pharmac's access criteria. The prescriber should also annotate the date of symptom-onset on every prescription so that the pharmacist can ensure that nirmatrelvir with ritonavir (Paxlovid™) or molnupiravir (Lagevrio®) can be initiated within five days of symptom onset.

Additional points for nirmatrelvir with ritonavir (Paxlovid™) include:

- Reviewing the potential for drug interactions and their appropriate management. The participating pharmacy may need to access a shared patient information database (e.g., Testsafe), or contact the general practice, patient, or patient's usual pharmacy if an up-to-date list of medicines is not readily available.
- Checking the therapy is appropriate where renal impairment is present. The prescriber should record the patient's most recent renal function (if available) on the prescription.
- Checking that any other contraindications have been identified and appropriately managed.

Pharmacists will need to contact the prescriber if there are any clinical issues with the prescription and resolve these collaboratively. Prescribers are asked to provide their contact phone number on the prescription.

If you cannot contact the prescriber, then you will need to contact the practice or care coordination hub. If there is an urgent after-hours query and the prescriber is not contactable, please phone the local DHB hospital operator or hospital duty manager team who will assist to locate the prescriber (if a hospital clinician), or a suitable back up.

How do I dispense nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®)?

The dispensing process for these medicines is largely the same as any medicine. The pharmacist will physically need to adjust the nirmatrelvir with ritonavir (Paxlovid™) whole-pack with the removal of some of the nirmatrelvir tablets for patients with renal impairment and ensure the instruction label states a renal dose.

Prescriptions should be processed as not subsidised (NSS).

How are nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) delivered to patients?

Pharmacies can use existing local courier networks to deliver oral COVID-19 therapeutics to patients. Pharmacies are encouraged to collaborated with local care coordination hubs if delivering these medicines to hard-to-reach areas is an issue. There will be local kaupapa Māori or Pacific providers who can help with distribution and delivery.

When counselling a patient:

- Provide them with a copy of the Health Navigator information sheet for nirmatrelvir with ritonavir (Paxlovid™) or molnupiravir (Lagevrio®)
- Confirm the patient understands how to take the medicine safety and appropriately
- Confirm pregnancy and breastfeeding status and the potential need to use contraception
- For nirmatrelvir with ritonavir (Paxlovid™), discuss management of drug interactions
- Advise them to contact the prescriber or pharmacy if they experience adverse events or worsening of condition.

How am I funded for supplying nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®)?

Nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) (and the delivery) are **free of charge** to eligible patients.

They are both listed as Xpharm on the Pharmaceutical Schedule, meaning pharmacies are not able to claim subsidy through normal claiming systems as alternative funding arrangements have been established. **There is no claiming through the routine pharmacy claiming systems**. Any claims that come through the usual channels for reimbursement will be declined.

COVID-19 Care in the Community funding will cover the costs of pharmacists' medicines management activities, and delivery of the medicine to the patient. There is no prescription co-payment associated with these medicines.

DHBs are responsible for setting up the contractual requirements to enable COVID-19 Care in the Community funding to pharmacies, so that Sector Operations can process the payments.

Do I need to dispense nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) to claim payment?

No. If the pharmacist completes a review and determines treatment to be contraindicated, otherwise inappropriate, or if the patient is not eligible, then they should discuss their concerns with the prescriber. If it decided to not proceed with dispensing, then the pharmacist can still claim the medicines management fee to acknowledge the time spent completing the review.

Can I supply nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) under a Practitioner's Supply Order (PSO)?

Only **practices in a rural area**[3] can be supplied nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lagevrio®) under a PSO.

However, prescriptions for these medicines must be retrospectively entered through the pharmacy dispensing system for data capture and reporting purposes.

Are there any other training resources I can access?

The Pharmaceutical Society of New Zealand has created a learning module for nirmatrelvir with ritonavir (Paxlovid™), which can be accessed here. A learning module for molnupiravir (Lagevrio®) will be released in early May.

The Patient Journey

How will I know if I'm eligible?

- There is advice for people with COVID-19 who are at higher risk on the Ministry of Health website.
- Your general practice team will be aware of your underlying conditions and will be in touch with you to assess your condition, and whether the treatment is suitable for you, once they know you are a COVID-19 case.
- If you are receiving COVID-19 care from a different healthcare provider, the healthcare provider will be alerted to your underlying conditions by the information you have provided on the COVID online self-assessment form.
- If you are not in the same locality as your enrolled general practice, are not enrolled with a general practice, and/or have not completed the online self-assessment form, the Care Coordination Hub will call you, or your local Health provider to assess your needs.
- It is important that you call your general practice or Healthline (0800 358 5453) if you are concerned about being severely unwell with COVID-19.

How will I get the medicine in time?

- Get tested as soon as symptoms develop. If you test positive for COVID-19, your Day Zero is the day you first experienced symptoms.
- Once you have received a text confirming your COVID-19 infection, if you are at risk of severe illness, you should have an initial clinical assessment by a health practitioner (such as your doctor, nurse practitioner or pharmacist prescriber) within 24 hours. Planning for your COVID-19 care will be done at the same time as this assessment.
- The prescription for a COVID-19 medicine will be sent directly to the participating pharmacy, who will arrange delivery of the medicine to you in time to start within 5 days of onset of symptoms. The participating pharmacy will also make contact with you to ensure you know how to take the medicine properly.

Will it cost me anything?

- No, the testing, clinical assessment, prescription, advice, and delivery are all covered by the COVID-19 Care in Community funding and are free to eligible patients.

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[1] Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, Pypstra R. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. New England Journal of Medicine. 2022 Apr 14;386(15):1397-408.

[2] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. New England Journal of Medicine. 2022 Feb 10;386(6):509-20.

[3] a rural area is defined by the Pharmaceutical Schedule as an area locally determined as rural by the appropriate DHB.