Te Whatu Ora
Health New Zealand

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

24 November 2022

Contents:

1.Introduction

Nirmatrelvir with ritonavir (Paxlovid) and molnupiravir (Lagevrio) are used to treat COVID-19 infections within the first 5 days of onset to reduce the risk of severe illness and hospitalisation. They are not used for the treatment of long COVID.

Paxlovid and molnupiravir have been available for prescribing and dispensing since 5th April and 4th May 2022 respectively.

The access criteria for oral COVID-19 antiviral medicines have been widened from the time they were first made available to allow greater access for more people who would be at risk of getting sicker. The most recent widening of the access criteria was on 14 September 2022 with the below Pharmac eligibility criteria:

1. Confirmed (or probable) symptomatic COVID-19,
2. OR has symptoms consistent with COVID-19 and is a household contact of a positive case;

AND

3. Symptoms started within the last 5 days;

AND

4. Does not require supplemental oxygen

AND any of the following:

5. Māori or Pacific people aged 50 years or older
6. everyone aged 65 years and older
7. anyone aged 50 years or older with fewer than two COVID-19 vaccinations
8. anyone with a severely weakened immune system
9. anyone with Down syndrome
10. anyone with sickle cell disease
11. anyone previously in critical or high dependency hospital care from COVID-19
12. anyone with three or more high-risk medical conditions.

Also, from 28th July 2022, pharmacists that have done extra training have been able to supply medicines without a prescription to eligible people with COVID-19 to enable greater access to these medications. Pharmacies supplying COVID-19 antivirals without a prescription can be found here. Paxlovid and molnupiravir were new to the market, and information about their prescribing and dispensing safety is important to consider. Particular care is needed to manage the clinically important drug-drug interactions of Paxlovid.

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.

Considerations for the forthcoming summer holiday season in Aotearoa New Zealand:

Consider how COVID-19 management processes will work for your patients over this Christmas/New Year holiday period and ensure that COVID-19 positive patients understand who they may need to contact if their condition deteriorates and how to access antivirals, if they qualify.

Ensure key stakeholders, like Healthpoint, hospices and community pharmacies, are aware of the practice's holiday hours and where you are directing patients when closed.

Ensure patients are aware of resources and community services that can aid them over this period, e.g., Healthpoint, Plunket line, Healthline, COVID-19 Health Hub, COVID line, Health Navigator resources (data free).

Ensure high risk patients have a plan if their condition deteriorates.

Indication

Paxlovid and molnupiravir are oral antivirals used to treat COVID-19 in the viral replication phase of the infection.

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 doses are 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 in most cases to prescribe Paxlovid or molnupiravir. When assessing eligibility, shared decision making between the primary care practitioner, patient, health providers and whānau is encouraged.

Paxlovid and molnupiravir may be prescribed in advance of testing positive for COVID-19, to be dispensed when the patient tests positive or becomes a probable case. To be eligible for an advance prescription for oral COVID-19 therapeutic agents, the patient must meet Pharmac eligibility criteria.

For an advance prescription to be dispensed, the patient must meet ALL of the Pharmac eligibility criteria (including the requirements relating to being a current COVID-19 confirmed or probable case).

See guidance here for special considerations for advance prescription for 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.

Private supply of COVID-19 therapeutics

Merck Sharp and Dohme have made available additional stock of molnupiravir for private supply pursuant to a prescription. Community pharmacies will be able to procure private supply of molnupiravir from their usual wholesaler. This will most likely be ordered on demand and pharmacies may not have stock available when a prescription is written. The cost of the medicine will have to be met by the patient. Pharmacists are not publicly funded to conduct medicines management activities or counsel patients who are privately purchasing COVID-19 therapeutics.

Paxlovid is not currently available for private supply.

Place in Therapy

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

The transferability of these findings to the current COVID-19 setting in Aotearoa is uncertain, however emerging evidence (see Centres for Disease Control and Prevention and British Medical Journal) suggests both Paxlovid and molnupiravir appear to maintain activity against Omicron and still have a place in therapy for those most at risk of severe outcomes.

There have been recent reports, yet to be peer-reviewed, that further support an approach to utilise Paxlovid more in those who are at risk of hospitalisation from COVID-19. Until the COVID-19 Therapeutics Technical Advisory Group forms a further position about these studies, this advice continues to reflect the latest advice.

Side effects for both drugs are usually mild and self-limiting.

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 must be within 5 days of symptom onset.

Dose adjustment of the nirmatrelvir component is necessary where there is moderate renal impairment, with eGFR 30-59ml/minute.

Some limited early data suggests a reduced dose Paxlovid in renal failure (eGFR < 30) may not be associated with significant harm. We recommend consideration of Paxlovid in

this population after careful risk-benefit assessment. There are some significant drug interactions with Paxlovid that prescribers need to check for before prescribing these medicines. However, consideration of the significant Paxlovid drug interactions is as applicable to patients with chronic kidney disease (CKD) as for those without any renal dysfunction. Consultation with the patient's renal physician or referring to HealthPathways is recommended. Risks of causing unintended harm due to changes to a patient's other regular medications, such as leading to subsequent medication omission, should be carefully considered, and mitigated against if Paxlovid is used. See Antiviral options for COVID-19 infection in patients with chronic kidney disease

No dose adjustment is required where there is mild hepatic impairment. Contraindications include those with severe hepatic impairment, and pregnancy.

See drug interaction guidance links in the 'Key Resources' section below.

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. Due to the short-term nature of Paxlovid therapy, however, many of these interactions can be managed. This is particularly important if the patient is at high risk of hospitalisation.

Depending on the severity of interaction and relative importance of the other drug, 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

Dosage
Molnupiravir 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 nor its active metabolite are inhibitors or inducers of major drug metabolizing enzymes or transporters. No significant drug interactions have been identified based on the limited available data.

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

2. Key Resources

- Pharmac Access Criteria
- Clinical guidance on HealthPathways Case Management in Adults pathways.
- The New Zealand Formulary (NZF) drug monographs for Paxlovid and molnupiravir
- He Ako Hiringa have a resource to guide review of drug interactions with Paxlovid and have also published a clinical resource for molnupiravir
- Paxlovid datasheet and molnupiravir datasheet
- Health Navigator have created plain-language consumer information leaflets for Paxlovid and molnupiravir, as well as a general overview of COVID-19 antivirals
- List of pharmacies that offer COVID-19 antivirals can be found on the Karawhuia website, or the Healthpoint website here (without a prescription) or here (with a prescription).

A recording of the HealthPathways webinar that focused on Paxlovid and molnupiravir can be found here.

3. Responsibilities

Distribution

- Paxlovid and molnupiravir are being distributed by the wholesaler to participating pharmacies. A list of each regions' participating pharmacies can be found on HealthPathways, Karawhuia website, or the Healthpoint website here (without a prescription) or here (with a prescription).

Prescribing

- Eligible patients will be identified and confirmed as meeting access criteria on the initial clinical assessment of the COVID-19 case.
- The prescriber or appropriately trained pharmacist have 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 considered 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 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 and/or prescriber where necessary to ensure patient safety. The pharmacy will dispense the medicine, provide advice to the patient, and organise delivery.

Monitoring

- Te Whatu Ora | Health New Zealand and Pharmac will review supply and COVID-19 case data to inform stock management, and quality control processes.
- It is important for pharmacists and prescribers to report any suspected adverse drug events to the Centre for Adverse Reactions Monitoring (CARM).

4. Process details

Prescriber/Supplier

How will 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 based on the person meeting eligibility criteria, and clinical presentation and symptoms onset. The assessment and prescribing activities are funded within the initial proactive assessment consultation.
- Many practices will already be aware of several of their patients who are most vulnerable (for example, the severely immunosuppressed include those who 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 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/supplying an oral COVID-19 antiviral therapeutic.

- Check whether the patient meets Pharmac's access criteria.
- Review suitability of the therapeutic, specifically any contraindications and whether the patient wants active intervention.
- Consider discussing the implications of treating with 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 Paxlovid:
    - Review renal function and consider dose adjustment if eGFR < 60 mL/minute within the last 3-6 months.
    - 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 Paxlovid (if applicable, renal function test should be within last 3-6 months),
- 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. Consumer information is available on the Health Navigator website for Paxlovid and molnupiravir.

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.

What happens if a patient develops 'COVID-19 rebound' after antiviral treatment?

- Rebound infection is seen in up to 10% of cases within the first 30 days and occurs in both patients who have taken antivirals and those who have not. It usually occurs within 2 weeks of initial COVID-19 onset but can occur up to 4 weeks after initial onset.
- Testing is not required.
- Advise the patient to stay at home if unwell. Isolation is not required but is recommended until 24 hours after symptom resolution.
- Further antivirals are not indicated. The patient is unlikely to become severely unwell; review if concerned.
- Recommend standard protective measures for household contacts.

What happens if a patient has a re-infection after antiviral treatment?
If a patient tests COVID-19 positive 29 or more days since a previous infection, this is considered to be a new infection and should be treated as such. Therefore, the prescribing of antivirals should be considered again.

Pharmacists

Who is the wholesaler?
Pharmac have contracted ProPharma as the community wholesaler for funded supply of Paxlovid and molnupiravir.

What are participating pharmacies?
There are around 400 participating pharmacies around the country who can order and supply funded Paxlovid and molnupiravir. The list of pharmacies that offer Covid-19 antivirals can be found on the Karawhuia website, or the Healthpoint website here (without a prescription) or here (with a prescription).

How do I order stock of funded Paxlovid or molnupiravir?
Stock can be ordered from ProPharma using standard processes.

If the supply of Paxlovid or molnupiravir becomes constrained, restrictions may be placed on ordering. Your district pharmacy portfolio manager will be able to offer guidance if this situation occurs.

What do I need to do when reviewing a script for Paxlovid or molnupiravir?
Every prescription must be reviewed for completeness and appropriateness. Unless contraindicated, patients requiring a COVID-19 oral antiviral should 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 access criteria. The prescriber should also annotate the date of symptom-onset on every prescription so that the pharmacist can ensure that Paxlovid or molnupiravir can be initiated within five days of symptom onset.

Additional points for 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.

How do I dispense Paxlovid and molnupiravir?
The dispensing process for these medicines is largely the same as any medicine. The pharmacist will physically need to adjust the 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 Paxlovid and molnupiravir delivered to patients?
Timeliness of delivery is important to ensure the medicines are received by the patient within 5 days of becoming a case. Pharmacies can use existing local courier networks to

deliver oral COVID-19 therapeutics to patients. Pharmacies are encouraged to collaborate 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 Paxlovid and molnupiravir.

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 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 Paxlovid and molnupiravir?
Paxlovid and molnupiravir (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 eligible patients. There is no prescription co-payment associated with these medicines.

District portfolio managers 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.

No payments will be made for services provided in relation to private supply of Paxlovid or molnupiravir.

Do I need to dispense Paxlovid and molnupiravir 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 has been prescribed). If it is 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 Paxlovid and molnupiravir under a Practitioner's Supply Order (PSO)?
Only **practices in a rural area**[3] can be supplied Paxlovid and molnupiravir 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 series of learning modules for COVID-19 Antiviral Training which can be accessed here.

The Patient Journey

How will I know if I am eligible?

1. There is advice for people with COVID-19 who are at higher risk on the COVID-19 Health Hub website.
2. Your general practice team or hauora provider 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.
3. If you are not in the same locality as your usual health provider, or do not have a usual health provider, 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.
4. It is important that you call your health provider 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.
- Report the result of a rapid antigen test (RAT) on My Covid Record, or by calling 0800 222 478 and choose option 3. You will then be sent a link to a free-data online form that you need to fill out. This form will allow you to provide information to your health team about any health needs you have.
- If you are at risk of severe illness, you will 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 contact 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.

Version Control

Version	Date	Author	Notes
1.5	July 2022	Care in the Community	
1.6	Nov 2022	Care in the Community	1. Added latest eligibility criteria 2. Added considerations for holiday period 3. Added pharmacist-only reclassification 4. Added advice supporting increased use of Paxlovid 5. Added guidance for dosing in chronic kidney disease (CKD) 6. Moderated advice on management of drug interactions with Paxlovid 7. Updated links to key resources 8. Updated advice on rebound infection and re-infection 9. Strengthened advice on timeliness of delivery 10. Clarified process for reporting COVID-19 positive results 11. Added advance prescription guidance 12. Clarified how recent renal function tests must be 13. Clarified eligibility criteria 14. Added not for use with Long COVID

[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.