Te Whatu Ora
Health New Zealand

Guidance on community use of oral COVID-19 antivirals

16 August 2023

Contents:

1.Background

Nirmatrelvir with ritonavir (Paxlovid), remdesivir (IV treatment) and molnupiravir have been used, in New Zealand, to reduce the risk of severe illness and hospitalisation from COVID-19 infections since April 2022. These medicines are not used for the treatment of long COVID.

The evidence around effectiveness of these medicines is continuously being reviewed and as we learn more, we need to change our approach. Accumulating evidence suggests that at the present time molnupiravir treatment is unlikely to be of benefit and is no longer recommended by the Ministry of Health COVID-19 Therapeutics Technical Advisory Group.

Paxlovid continues to be the first-line antiviral for the treatment of COVID-19 as supported by the current clinical guidance from the Ministry of Health COVID-19 Therapeutics TAG.

2.Guidance

Eligibility criteria for COVID-19 antivirals

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 higher risk of poorer health outcomes from COVID-19, particularly hospitalisation and death. Studies have also shown that people with COVID-19 at standard risk, especially when further lowered by vaccination, would have minimal or no benefit from oral antivirals.

The most recent widening of the access criteria was on 14 September 2022 and the Pharmac access criteria can be found here.

Antiviral options

Paxlovid (oral), remdesivir (IV) and molnupiravir (oral) are antivirals which have been available to treat COVID-19 in the viral replication phase of the infection.

Evidence suggests that Paxlovid is effective against the Omicron variants in reducing the development of serious illness and hospitalisation in those who are most at risk, in

vaccinated populations[i] [ii] [iii] [iv]. However, recent evidence suggests that molnupiravir is unlikely to be of benefit[v] and the use of molnupiravir is no longer recommended by the Ministry of Health COVID-19 Therapeutics Technical Advisory Group.

Remdesivir is the recommended 2nd line treatment, in regions where this service is available (for non-hospitalised patients).

It should be noted that the COVID-19 vaccination booster doses are very effective in reducing the rate of hospitalisation and should be prioritised for all of those that are eligible and especially for those with higher risk conditions.

Assessing patients

An in-person consultation is not needed in most cases to prescribe or initiate COVID-19 antivirals. When assessing eligibility, shared decision making between the primary care practitioner, the patient, other health providers and whānau is encouraged.

COVID-19 antivirals may be prescribed in advance to patients who meet all the Pharmac access criteria except for being a confirmed or probable case.

For an advance prescription to be dispensed, the patient must meet ALL of the Pharmac access 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 the Pharmac access criteria will not 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.

Particular care is needed to manage the clinically important drug interactions with 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. When drug interactions or the risks of temporary modification of regular medication regimens are assessed to outweigh the benefits of Paxlovid, it will then be the case that no oral antiviral is warranted now that molnupiravir is no longer recommended. Consideration should be given to the use of remdesivir 2nd line, in regions where this service is available (for non-hospitalised patients).

Private supply of COVID-19 therapeutics

Paxlovid is not currently available for private supply.

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.

Precautions and Interactions
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) is not associated with significant harm. We recommend consideration of Paxlovid in this population after careful risk-benefit assessment.

Consultation with the patient's renal physician or referring to HealthPathways is recommended. See Antiviral options for COVID-19 infection in patients with chronic kidney disease

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 for some of the patient's usual medicines.

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

Careful consideration is necessary to weigh the potential benefits versus risks of temporarily halting regular medicines and treating the COVID-19 infection. Risks of causing unintended harm due to changes to a patient's other regular medicines, such as failure to restart regular medicines on completion of the Paxlovid course, should be carefully considered, and mitigated against.

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.

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

Considerations for public holidays in Aotearoa New Zealand:

Consider how COVID-19 management processes will work for your patients on public holidays and long weekends and ensure that COVID-19 positive patients understand who they may need to contact if their condition deteriorates and how to access antiviral medicine, if they qualify.

Ensure key stakeholders, like Healthpoint, hospices, ARC facilities 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, Health Navigator resources (data free), COVID-19 Health Hub, Plunket line, Healthline and COVID line.

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

3. Key Resources

- Pharmac Access Criteria
- Clinical guidance on HealthPathways Case Management in Adults pathways.
- COVID-19 drug interaction checker
- The New Zealand Formulary (NZF) drug monograph for Paxlovid.
- He Ako Hiringa has a clinical resource forPaxlovid.
- Paxlovid datasheet.
- Health Navigator have created plain-language consumer information leaflet for Paxlovidas 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).
- Pharmaceutical Society of New Zealand COVID-19 Antivirals Training Programme available here

4. Responsibilities

Distribution

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

Prescribing/Initiating

- Eligible patients will be identified and confirmed as meeting access criteria on the initial clinical assessment of the COVID-19 case.
- The prescriber or initiating pharmacist 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 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 dispensing pharmacy will ensure, 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 pharmacy supplying the COVID-19 antiviral 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 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).

5. Process details

Prescriber/Supplier

Identifying cases who are at higher risk of hospitalisation

- Primary care may identify the COVID-19 cases that would benefit from an initial clinical assessment utilising local knowledge, digital tools and the PMS (where available). Practices could consider proactively reaching out to their patients that would be eligible for anti-viral therapy to advise then how to seek these medicines if they test positive for COVID-19
- Many practices will already be aware of 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.
- The eligibility for treatment will be determined based on the person meeting access criteria, and clinical presentation and symptoms onset. The assessment and prescribing activities are funded within the initial proactive assessment consultation, for those that are eligible cases.
- For cases that are not enrolled with a local general practice, they will be prioritised for a call from the Care Coordination Hub (if operating within your region) 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 medicine, specifically any contraindications and whether the patient wants active intervention.
- Consider discussing the management of Paxlovid interactions with medicines initiated in secondary care with the relevant specialist, e.g. Nephrologist, oncologist.
- Consider the advice needed for 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 or supplying 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, noting that the safety of the medicine is now more well-established and not having a current renal function test is not a requirement to initiate treatment),

- 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.

What needs to happen next?

- Active case management will include regular review for those in the eligible groups and if deemed to be at higher clinical risk by the clinician. The remaining population will be educated on when to appropriately seek further clinical advice based on their symptoms.
- 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 COVID-19 antivirals are not indicated. The patient is unlikely to become severely unwell; review if concerned, especially if the patient is immunocompromised.
- 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 COVID-19 antivirals should be considered again.

Supply through community pharmacies

Who is the wholesaler?

Pharmac have contracted ProPharma as the community wholesaler for funded supply of COVID-19 antivirals.

What are participating pharmacies?

There are around 700 participating pharmacies around the country who can order and supply funded COVID-19 antivirals. 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 Covid-19 antivirals?

Stock can be ordered from ProPharma using standard processes.

If the supply of COVID-19 antivirals 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 COVID-19 antivirals?
Every prescription must be reviewed for completeness and appropriateness. Unless contraindicated, patients requiring a COVID-19 oral antiviral should be offered Paxlovid.

All prescriptions must be endorsed that the patient meets Pharmac access criteria. The prescriber should also annotate the COVID-19 positive status and date of symptom-onset on every prescription so that the pharmacist can ensure that treatment 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 required) 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 or the Whakarongorau Clinical Advice line

How do I dispense COVID-19 antivirals?
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 COVID-19 antivirals delivered to patients?
When required timeliness of delivery is important to ensure the medicines are received by the patient within 5 days of symptom onset. Pharmacies can use existing local courier networks to deliver oral COVID-19 therapeutics to patients.

When counselling a patient:
Provide them with a copy of the Health Navigator information sheet for Paxlovid.

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.

Can I supply COVID-19 antivirals under a Practitioner's Supply Order (PSO)?
Only **practices in a rural area**[vi] can be supplied COVID-19 antivirals on 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.

6. 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
1.7	Mar 2023	Care in the Community	1. Removed references to Molnupiravir in line with updated clinical guidelines
1.8	Aug 2023	Care in the Community	1. Removed isolation and delivery advice

[i] Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. 2022. 1397-408]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2118542.
[ii] Schwartz K, Wang J, Tadrous M, Langford B, Daneman N, Leung V, et al. Real-world effectiveness of nirmatrelvir/ritonavir use for COVID-19: A population-based cohort study in Ontario, Canada. 2022. 2022.11.03.22281881]. Available from: https://www.medrxiv.org/content/medrxiv/early/2022/11/05/2022.11.03.22281881.full.pdf.

[iii] Aggarwal NR, Molina KC, Beaty LE, Bennett TD, Carlson NE, Ginde AA. Real-world Use of Nirmatrelvir-Ritonavir in COVID-19 Outpatients During the Emergence of Omicron Variants BA.2/BA2.12.1. 2022. 2022.09.12.22279866]. Available from: https://www.medrxiv.org/content/medrxiv/early/2022/09/15/2022.09.12.22279866.full.pdf.

[iv] Shah MM JB, Plumb ID, et al. Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 — United States, April–September 2022. MMWR Morb Mortal Wkly Rep 20222022. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e2.htm#suggestedcitation.

[v] Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial The Lancet2022 [updated 22 December 2022 Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02597-1/fulltext#%20.

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