Therapeutics Technical Advisory Group | Te Rōpū Haumanu Kowheori-19

Information and guidance for secondary care clinicians: antiviral agents for treatment of COVID-19

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The Therapeutics Technical Advisory Group (Therapeutics TAG) was established by the Ministry of Health in August 2021 to provide expert advice on existing and emerging medicines for use in the management of COVID-19.

Contents

1. Introduction

Background

There are currently three antivirals available in Aotearoa for the treatment of COVID-19 infection. The two oral antivirals are Medsafe approved medications, while remdesivir is currently available as an unapproved medication under Section 29:

- Nirmatrelvir with ritonavir (Paxlovid™), oral
- Molnupiravir (Lageviro®), oral
- Remdesivir, intravenous

Antivirals are most efficacious when prescribed early (as soon as possible and within 5 - 7 days of symptom onset) in the COVID-19 illness as they target the viral replication phase of the infection. Current evidence[1] suggests these antivirals are effective against the Omicron variant in reducing the development of serious illness and hospitalisation in those who are most at risk. Most of the prescription and dispensing of the oral antivirals is anticipated to occur in the community.

Identification of high risk, eligible patients in the community to allow timely access to the antivirals requires a multi-pronged approach. There is a need for therapeutic awareness amongst primary and secondary care

clinicians as well as at risk individuals in the community. A variety of strategies are being used in primary care. Barriers to appropriate antiviral treatment include community and prescriber awareness, early access to accurate testing, notification of test results and timely access to healthcare.

2. How can secondary care clinicians help?

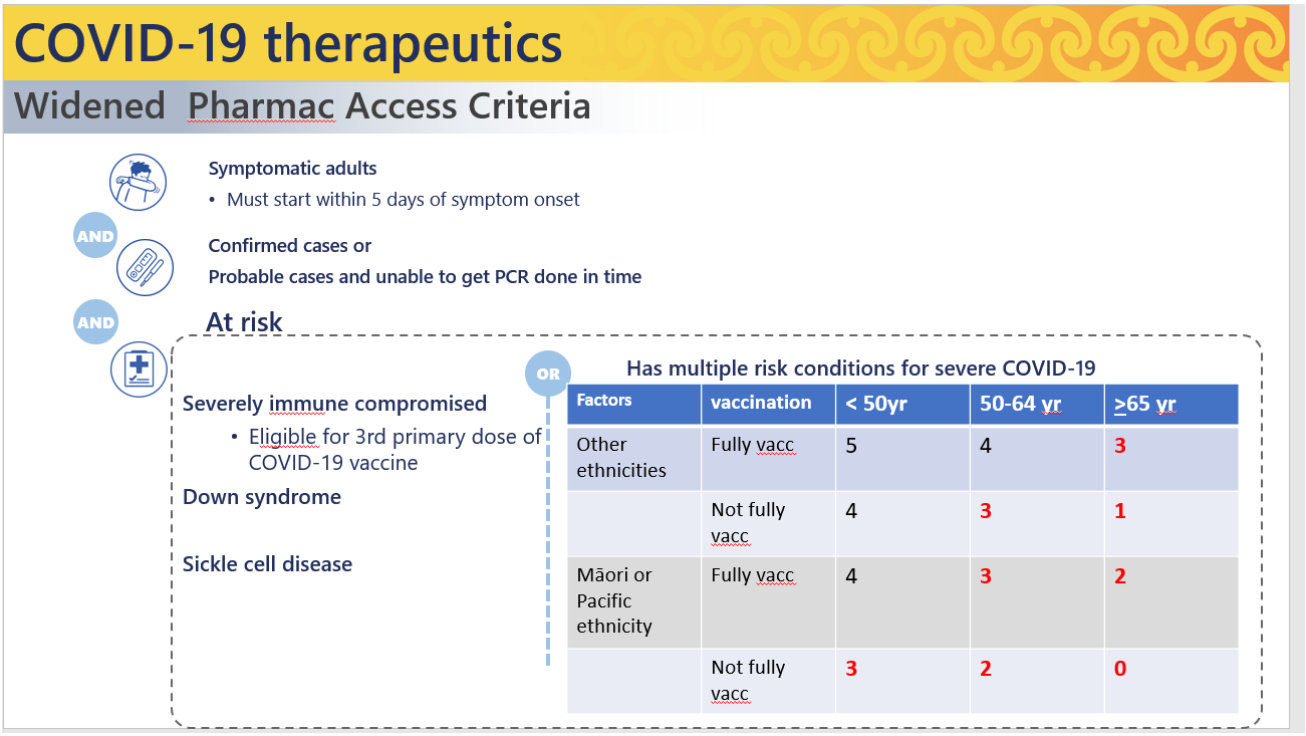
Within secondary care, many specialty teams will already be aware and have frequent contact with their high-risk patients, which presents an opportunity for raising therapeutic awareness. For instance, immunocompromised patients such as transplant recipients and patients on immunosuppressant drugs, would qualify (and benefit) from early antiviral therapy. Elderly patients, Māori and Pacific patients and those with multiple comorbidities may often also be at risk and eligible, especially if incompletely vaccinated. Through their specialist teams*, these patients and their GP could be advised about the availability of the oral antivirals* in the event they acquire COVID-19 infection, to allow timely access to treatment which can reduce their risk of progressing to severe COVID-19 illness. Patients should be advised to test as soon as they develop symptoms and to alert their GP if their tests return positive for COVID-19.

For people with early COVID-19 who are assessed in the Emergency Department or in an outpatient setting, arranging a prescription for an oral antiviral to be dispensed from an approved pharmacy is an option which may enable timely receipt of treatment.

3. Access criteria

The same access criteria apply to the three antivirals. The aim of the access criteria is to provide access to the people with the greatest risk of hospitalisation from COVID 19 and identifies people according to a combination of underlying conditions, age, vaccination status and ethnicity. They apply to people with mild-moderate COVID-19 infection regardless of whether they are inpatients or outpatients.

Pharmac's criteria for access to antiviral therapy updated as of 5 May 2022 can be found here. The infographic (below) and the Pharmac eligibility calculator tool (link here) are also available to aid the use of the access criteria.



NZ Ministry of Health list of higher risk medical conditions (link)

4. Prescribing considerations

Nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lageviro®) are new to the market, and information about their prescribing and dispensing safety is important to consider.

Which antiviral?

Available evidence demonstrates that nirmatrelvir with ritonavir (Paxlovid™) is considerably more effective than molnupiravir (Lageviro®) at reducing the risk of hospitalisation.[2,3] 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. If nirmatrelvir / ritonavir (Paxlovid™) is contraindicated or unavailable, remdesivir should be considered in preference to molnupiravir, where there are established mechanisms for accepting community referrals for this intravenous-only medication. Discussion with local infectious diseases team is recommended if uncertain.

Drug-drug interactions

The use of nirmatrelvir with ritonavir (Paxlovid™) is complicated by the significant number of clinically important drug-drug interactions. Prescribers are referred to the resources below to determine eligibility, manage potential drug interactions and access guide on how to prescribe. Potential interactions may be manageable by strategies such as temporarily withholding the usual medication, whilst some will on balance preclude use. Useful resources for managing drug interactions include pharmacists, the NZ Formulary and Liverpool Interactions Guide (see Resources).

No drug interactions for molnupiravir (Lageviro®) have been identified based on the limited available data.

Pregnancy

Nirmatrelvir with ritonavir (Paxlovid™) and molnupiravir (Lageviro®) are contraindicated in pregnancy.

a. 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.

b. Molnupiravir (Lageviro®)

Dosage

Molnupiravir (Lageviro®) 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

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

Neither molnupiravir (Lageviro®) 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.

5. Resources

- Pharmac Access criteria (link)
- Pharmac Access criteria assessment tool (link)
- Information for health practitioners Paxlovid (link) and molnupiravir (link)
- He Ako Hiringa guide on drug interactions with nirmatrelvir with ritonavir (Paxlovid™)
    - University of Liverpool COVID_19 interactions checker (link)
    - Ontario Science brief (link)
- New Zealand Formulary (NZF) Nirmatrelvir with ritonavir (link) and molnupiravir (link)

References

1. Wong C, Au I,Lau K, Lau E, Cowling B, Leung G. Real-world effectiveness of molnupiravir and nirmatrelvir/ritonavir among COVID-19 inpatients during Hong Kong's Omicron BA.2 wave: an observational study. MedRxiv preprint

2. 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.

3. 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.