

Antiviral Options for COVID-19 Infection in Chronic Kidney Disease – Therapeutics TAG position statement

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The Manatū Hauora COVID-19 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.

Update relating to change in clinical guidance for molnupiravir

- Paxlovid remains the first-line treatment in patients without contraindications, while remdesivir is the recommended second-line treatment.
- Clinical evidence to date suggests that molnupiravir likely has no clinical benefit in highly vaccinated populations against the current Omicron variants. This aligns with the current situation in Aotearoa New Zealand.
- On 24 February 2023 the Manatū Hauora COVID-19 Therapeutics TAG removed its recommendation to use molnupiravir in Aotearoa New Zealand. The rationale supporting this change can be found in a position statement ([link](#))

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Context of COVID-19 in Aotearoa New Zealand

SARS-CoV-2 Omicron variants have spread widely in the Aotearoa New Zealand community during 2022, peaking in the winter. **As of March 2023, a several immune-evasive Omicron variants, with no single dominant lineage, are in circulation in Aotearoa New Zealand. [1]** Risk factors for hospitalisation and mortality have included increasing age, vaccination status, comorbidities (particularly when multiple), and Māori or Pacific ethnicity. **The risk of hospitalisation overall has been less with Omicron than for earlier variants, particularly in those who are fully vaccinated. [2]** A

bivalent COVID-19 vaccine booster dose is currently being rolled out ahead of the 2023 winter. COVID-19 vaccination booster doses are very effective in reducing the rate of hospitalisation and should be prioritised for all eligible people and especially for those with higher risk conditions.

COVID-19 Antivirals Available in Aotearoa New Zealand

The antivirals Paxlovid (oral), remdesivir (IV) and molnupiravir (oral) remain available for the treatment of COVID-19 in Aotearoa New Zealand for people who meet the Pharmac clinical risk criteria.

Paxlovid remains the recommended first line treatment. Evidence has indicated 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 patients with contraindications to Paxlovid, remdesivir is the recommended second line treatment, where available, and the clinical risk is assessed to be very high.

Early clinical trial evidence in an unvaccinated population pre-Omicron indicated that molnupiravir had a lesser benefit in preventing (~30%) hospitalisation in high-risk (but not standard-risk) cases, and as such it was recommended as an option after Paxlovid and remdesivir. However, a recent very large UK trial of people with Omicron infection found no significant reduction in hospitalisation or death. On the balance of evidence to date, the use of molnupiravir is no longer recommended ([link](#)).

Chronic Kidney Disease and Risk of Adverse Outcomes from COVID-19

Chronic kidney disease (CKD) is associated with an increased risk of hospitalisation, mortality, and other adverse outcomes from COVID-19 infection. For example, one systematic review showed an increased risk of hospitalisation in patients with CKD and COVID-19 (RR = 1.63, 95% CI 1.03–2.58). [3]

Vaccination substantially reduces the risk of hospitalisation associated with COVID-19 in the general population and most people with CKD appear to respond to the vaccination, with the development of protective antibodies. Haemodialysis and kidney transplant patients have reduced humoral and cellular immune responses when compared to healthy controls. However, the immune response from haemodialysis patients improves greatly, reaching near healthy-control levels, when patients are fully up-to-date with vaccination (e.g., two primary and one booster dose). The lower immune response among kidney transplant patients also improved but remained significantly lower than healthy controls.

The response to vaccination appears to be reduced in people with renal transplants on some anti-rejection medications (e.g., mycophenolate). [4] Some renal transplant patients have developed persistent COVID-19 infection and have difficulty with clearing the virus. Overall, post-COVID syndrome (generally known as 'long COVID') is relatively common following infection, but it is currently unknown whether it is more common in patients with CKD or whether antiviral therapies reduce the occurrence.

Effectiveness at Preventing Hospitalisation

Phase 3 clinical trials of the agents available in Aotearoa New Zealand were conducted in the pre-Omicron era and mostly in unvaccinated and COVID-19-naïve patients. Patients with stage 4 CKD and a GFR<30 mL/min were excluded from these trials. The trials showed a significant reduction in hospitalisation when given to patients at increased risk early after the onset of COVID-19 symptoms. [5-7] In general these medicines are well tolerated with a good safety profile.

In general, Paxlovid and remdesivir were considerably more effective at preventing hospitalisation (>85%) than molnupiravir (~30%). The antiviral activity of these agents is thought to be retained in patients with Omicron variant infections.

Options for Treatment in Renal Failure

Medications must be looked at very carefully, as patients with CKD are likely to be on multiple regular medications.

Nirmatrelvir and ritonavir (Paxlovid™)

Patients with moderate to severe renal impairment were excluded from the main clinical phase 3 EPIC-HR study of Paxlovid™ use in non-hospitalised patients. [5] However, some data and experience of dose-adjusted use of Paxlovid™ has recently been published from Ontario and has been included in the Ontario treatment guidelines. [8, 9]

We note the reduced dosing regimen is pragmatic, and appears duly cautious, noting the effectiveness could differ from the EPIC-HR study results. 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.

The Aotearoa New Zealand Paxlovid™ datasheet wording uses 'contraindicated', which differs subtly from 'not recommended' in the FDA EUA Fact Sheet. [10, 11] The reason given in the datasheet was a lack of data in renal failure, and that appropriate dosage for patients with severe renal impairment had not yet been determined.

From data available to date, there does not appear to be evidence of harm from dose-reduced use of Paxlovid™ in renal failure (eGFR < 30). A phase 1 dosing study among health volunteers reported Paxlovid™ was safe and well-tolerated in single-ascending dose, multiple-ascending dose, and supratherapeutic cohorts. [12] Ritonavir has a long track history of use in HIV infection, similarly with a 100mg dose to 'boost' the level of another protease inhibitor. In that setting ritonavir has been found safe when taken by patients often over years. The relatively short standard treatment course of 5 days should also reduce any risk of major drug accumulation. Both common (diarrhoea, vomiting, dysgeusia, headache) and uncommon (myalgia, hypertension) reported side-effects of Paxlovid™ are usually relatively easy to clinically manage.

Considerations of the significant Paxlovid™ drug interactions are as applicable to patients with CKD as for those without any renal dysfunction. 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. A summary of the use of Paxlovid™ in CKD can be seen in Table 1 below

Table 1 Nirmatrelvir and ritonavir (Paxlovid™) in CKD

Kidney failure	eGFR (mL/min)	Dosage (NB: 150mg nirmatrelvir tablets)
Nil	≥90	(nirmatrelvir 300mg + ritonavir 100mg) po q12h for 5 days
Mild	60 - 89	As above, no dose reduction
Moderate	30-59	(nirmatrelvir 150mg + ritonavir 100mg) po q12h for 5 days
Severe	<30	<i>Consider</i> (nirmatrelvir 300mg + ritonavir 100mg po) daily on day 1, then (nirmatrelvir 150mg + ritonavir 100mg po) daily for 4 days
PD or HD		<i>Consider</i> , with dose as for eGFR <30 ml/min, but dose after dialysis. Strongly recommend decision on use to be made in conjunction with the renal dialysis team
Renal transplants		Avoid, unless on advice from patient's transplant specialist ¹ .

Abbreviations: po = per oral, PD = peritoneal dialysis, HD = haemodialysis, q12h = every 12 hours, eGFR = estimated glomerular filtration rate

- Suggested dosing for weight <40kg [here](#).
- Use barrier contraception for 7 days after last dose
- Do not prescribe Paxlovid™ for **'rebound' COVID-19**

Remdesivir (Veklury™).

While the PINETREE study showed that 3 days of intravenous remdesivir was effective in reducing hospitalisation, [7] use of remdesivir in Aotearoa New Zealand is largely constrained to being hospital-based. The WHO Solidarity trial showed a modest benefit in non-ventilated hospital inpatients against death or progression to ventilation (or both). [13] Remdesivir has an advantage of few drug-drug interactions. With remdesivir, the excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with reduced renal function. Caution is advised if eGFR is less than 30 mL/min/1.73m², with several international regulators advising against use due to a lack of information. In a case series of people with CKD on haemodialysis, remdesivir was well tolerated. [14, 15] Pharmacokinetic analysis suggest that in patients with reduced renal function 2 days of treatment is expected to provide equivalent concentrations to the 3-day regimen in patients with normal renal function.[16, 17]

Molnupiravir (Lagevrio™)

Although molnupiravir is a relatively well tolerated and safe option, and presently remains funded by Pharmac, it is no longer recommended for treatment of COVID-19 by the Manatū Hauora Therapeutics TAG.

Specialist Advice

Specialist advice may be helpful to discuss the risk/benefit of COVID-19 antiviral therapeutics for individual patients with CKD. Relevant specialists include infectious diseases physicians, clinical microbiologists, renal physicians, and renal transplantation specialists. Such advice should usually be sought for patients on renal dialysis or with transplants.

¹ Due to significant interactions with anti-rejection medications.

Abbreviations:

CKD: Chronic Kidney Disease

eGFR: estimated Glomerular Filtration Rate

HD: Haemodialysis

PD: Peritoneal Dialysis

po: per oral

q12h: every 12 hours

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