Record of the COVID Treatments Advisory Group Meeting held on 14 February 2023

The role of Advisory Groups and records of meetings

Note that this document is not necessarily a complete record of the COVID Treatments Advisory Group meeting; only the relevant portions of the meeting record relating to COVID Treatments Advisory Group discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

The COVID Treatments Advisory Group may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule; or

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule; or

(d) recommend that Pharmac discontinue funding of a pharmaceutical currently on the Pharmaceutical Schedule.

Advisory Groups give advice to Pharmac, including recommendations', based on the Groups' different, if complementary, roles, expertise, experience, and perspectives. Recommendations made by the COVID-19 treatments Advisory Group are in the context of COVID-19 treatments only. Pharmac is not bound to follow the recommendations made below.

The record of this Advisory Group meeting will be reviewed by PTAC at an upcoming meeting.

Attendance

Present
Chair – Dr Jane Thomas
Professor Brian Anderson
Eamon Dufy
Dr Gillian Hood
Dr Justin Travers
Dr Marius Rademaker
Dr Nigel Raymond
Dr Robyn Manuel
Professor Stephen Munn

Apologies
Dr Graham Mills
Dr Jessica Keepa
Dr Kerry Benson-Cooper
Dr Tim Cutfield

1. Nirmatrelvir with ritonavir cost effectiveness

Application

1.1. The Advisory Group reviewed the information relating to the cost effectiveness of nirmatrelvir with ritonavir for the treatment of COVID-19.

1.2. The Advisory Group took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Discussion

Acknowledgement

1.3. The Advisory Group acknowledged again the particular impact of COVID-19 on Māori and Pacific people, older people, people who are immunocompromised, people with premorbid conditions (eg. lung disease, diabetes, heart disease, etc), and/or disabled people.

Māori impact

1.4. The Advisory Group discussed the impact of funding nirmatrelvir with ritonavir for the treatment of COVID-19 for Māori, and the subsequent separate event rate-based cost-effectiveness analysis undertaken for Māori in each age group. The Group noted that there were some limitations in the data used in the analysis, where unified data combining cases with both hospitalisations and death was stratified by age or ethnicity but not both age and ethnicity. The Group noted that the subgroup analysis employed an increased risk of hospitalisation or death for Māori due to COVID-19, given previous advice and evidence that suggested Māori are at increased risk of severe disease. The Group noted that any separate analysis undertaken for Māori would be subject to a high degree of uncertainty given the data limitations.

Background

1.5. The Advisory Group noted that this was a rapid cost utility analysis for the use of nirmatrelvir with ritonavir (Paxlovid) and considered health outcomes while excluding indirect cost outcomes (eg productivity costs) for individuals using nirmatrelvir with ritonavir. The Group noted that this was an initial analysis based on Manatū Hauora - Ministry of Health data on mortality and reported cases. The Group noted that there were some limitations in the stratification of the data, where that data was stratified by age or ethnicity but not both age and ethnicity. The Group noted that due to this limitation analyses were undertaken by age and ethnicity separately, given previous advice that Māori and Pacific peoples are at increased risk of severe disease.

1.6. The Advisory Group noted that economic benefit to individuals, such as being able to get back to paid employment faster, are not considered in the cost-effectiveness analysis, consistent with the policies in Pharmac's current Prescription for Pharmacoeconomic Analysis (PFPA). The Group noted that being able to return to normal activities is considered in quality of life assessment, which could include paid work.

1.7. The Advisory Group noted that the evidence base for COVID-19 and its treatments is fast changing and has significant variability, resulting in significant uncertainty with the analysis undertaken regarding nirmatrelvir with ritonavir cost effectiveness.

Health need

1.8. The Advisory Group noted its previous advice that likely under-reporting of positive COVID-19 may overestimate the true case hospitalisation and mortality rates, and that calculated case-specific outcome rates based on reported case numbers were likely over-estimations of the actual hospitalisation and mortality rate. The Group was informed of anecdotal reporting from one region, that of those presenting to pharmacy for antiviral treatment up to 25% had not reported themselves or otherwise been reported as a RAT-positive case on the covid19.govt.nz website. The Group considered that there are barriers for some populations reporting either themselves or on behalf of others as a positive case as previously considered by the Group. The Group considered that the under-reporting of COVID-19 cases was not due to pharmacist-only supply of COVID-19 therapeutics, as the Covid Clinical Care Module (CCCM) system reports a case when pharmacist supply is recorded within the system, thereby supporting reporting.

1.9. The Advisory Group noted that the current access criteria allow for use of nirmatrelvir with ritonavir in those who are a likely case, ie a household contact with symptoms consistent with COVID-19, but do not yet have a positive rapid antigen test (RAT) and therefore are not able to be reported as a positive case. The Group considered this was to facilitate timely initiation of treatment, due to the significant impact of time to initiation on treatment efficacy The Group considered that this group of household contacts was the most likely group to receive nirmatrelvir with ritonavir without being formally reported as a case. The Group noted that the creation of a case in the CCCM system is not required for GP to prescribe, and while primary care is encouraging uploading of test results it is widely accepted that there is little time to prioritise this.

Health benefit

1.10. The Advisory Group noted that the pivotal EPIC-HR trial (Hammond et al. N Engl J Med. 2022; 386:1397-408) provided the primary outcomes of reduction in hospitalisation and

mortality within 28 days after infection and was the basis for the initial access criteria. The Group noted that the EPIC-HR trial was conducted in 2021 while the Delta variant was circulating, in an unvaccinated population who were at high risk of severe disease due to age or specified comorbidities. The Advisory Group considered that the absolute results from the EPIC-HR trial could not be applied to lower risk populations, due to the good vaccination coverage in the population and different SARS-CoV-2 variant circulating at the time of the trial, with both of these variables likely resulting in an appreciably lower absolute risk of hospitalisation and death.

1.11. The Advisory Group noted the EPIC-SR (ClinicalTrials.gov Identifier: NCT05011513) trial of standard risk patients. The Group noted this trial was terminated due to the very low absolute risk of hospitalisation or death in either arm of the trial, as well as the primary endpoint of four consecutive days symptoms free not being met. The Group also noted that Pfizer had released interim results reporting that there was a 51% decrease in the risk of hospitalisation or death, however this finding was not statistically significant. The Group considered that the failure to meet the primary endpoint does not necessarily suggest that there is no symptom alleviation benefit in those people with lower risk, and that there could be a reduction in symptoms of less than four consecutive days of symptoms. However, the Group noted that there was little evidence to inform whether there was a symptom relief benefit. The Group further considered that if short-term symptom relief was included as a benefit in the modelling, that the adverse effect profile of nirmatrelvir with ritonavir must also be considered, due to the potential harm or adverse effects that people may experience with this treatment. The Group also considered that the placebo effect for those using a COVID-19 treatment without severe symptoms was potentially impactful, however did not have data relating to the impacts of this with nirmatrelvir with ritonavir specifically.

1.12. The Advisory Group considered that it was important that the benefits of nirmatrelvir with ritonavir include non-hospital mortality, as there is likely to be significant mortality that occurs outside of hospital particularly for older people.

1.13. The Advisory Group considered two non-experimental observational cohort studies from the Omicron era and the association between nirmatrelvir with ritonavir and mortality from the United States (Dryden-Peterson et al. Ann Intern Med. 2023;176(1):77-84) and Israel (Arbel et al. N Engl J Med 2022;387:790-8). The Group considered that although these studies were cohort studies rather than randomised controlled trials, these studies were likely more relevant to the current New Zealand context than the EPIC-HR and EPIC-SR studies, due to the size of the populations included and consequent power, and the studies being conducted in the Omicron variant era with highly vaccinated populations. The Group considered the assessment of cause of death within these studies could potentially include deaths unrelated to COVID-19 infection, but considered the size of the untreated arm compared to the treated arm would detect late deaths in both groups. The Group considered the subgroups in the analysis were not well defined, but that the recent observational evidence indicated a likely greater magnitude of benefit with nirmatrelvir in those aged over 65 years compared to those under 65 years.

1.14. The Advisory Group discussed post-acute mortality (ie mortality more than 28 days after initial COVID-19 infection). The Group noted that post-acute mortality was estimated by

Pharmac staff to comprise one-third of COVID-19 associated deaths, and noted that this was a key point of uncertainty given the evidence base. The Group considered that there was likely some risk of post-acute mortality associated with COVID-19 that was not accounted for in the EPIC-HR or EPIC-SR studies. The Group considered that other viral infections such as herpes zoster (Shingles) have an increased mortality rate for 6 to 12 months, and this typically impacts those in older age groups (e.g. 70+) due to the increase in fragility that accompanies infection. The Group considered that some older patients with COVID-19 may present late with pneumonitis, but that this was more common with earlier variants of COVID-19. The Group considered that one third post-acute mortality would potentially apply to people of older age that are at higher risk of severe COVID-19.

1.15. The Advisory Group noted evidence reporting post-acute mortality during the pre-Omicron era for those with severe COVID-19, was estimated as 50% mortality within the first 12 months post-infection. The Group noted that this was early on in the pandemic, when outcomes were poor with severe COVID-19, especially if leading to ICU, in populations with known increased mortality. The Group considered such mortality rates depend heavily on the population studied, country, ICU facilities (and admission criteria etc), severity of illness scoring, and morbidity co-factors.

1.16. The Advisory Group noted that Manatū Hauora - Ministry of Health had reported late deaths (after 28 days) as comprising 2.7% of all COVID-19 attributed deaths, as at 12 February 2023. The Group noted the significant discrepancy between historical literature and the potential rate as reported, and considered that for the overall population, post-acute mortality would be lower than one third of all COVID-19 deaths. The Group considered, in general, that the mortality rate was significantly lower with Omicron variants compared to earlier variants and that this was likely to apply to post-acute mortality as well. An Observer noted that the Public Health Agency (PHA) may have further data with further detail relating to mortality internationally and nationally. The Group also considered that there were impacts from COVID-19 on other services – such as delays in accessing timely treatment for other conditions – and that this could result in excess mortality beyond the acute infection period.

1.17. The Advisory Group noted evidence of efficacy of nirmatrelvir with ritonavir in reduction of post-acute sequelae (long COVID) or post-acute death (after 28 days).

1.17.1. The Group noted a preprint retrospective cohort study in US Veterans (Xie et al. Preprint. 2022) reported that there was a reduction in post-acute death of 48%, post-acute hospitalisation 30% and post-acute sequelae 26%.

1.17.2. The Group noted that there were limitations of this study, including that this was a non-experimental observational cohort study rather than a randomised controlled trial; that it included only those that were considered at high risk of severe outcomes; and that the definition of post-acute sequelae (long COVID) was different to New Zealand definitions of long COVID.

1.18. The Advisory Group also considered that the definition of long COVID was not clear and that there are many people presenting post COVID-19 with fatigue-like syndromes. The Group considered that a decrease in the severity of illness associated with Omicron

variant infection could also mean there is a decrease in morbidity of post-acute sequelae (long COVID) but considered this was not currently supported by evidence.

1.19. The Advisory Group considered that efficacy of nirmatrelvir with ritonavir in reducing morbidity associated with long COVID would be difficult to assess, due to lack of confidence in diagnosis of long COVID, different definitions of long COVID, and difficulties with assessing a more subjective endpoint. The Group considered that there are other viral infections that have extended recuperation periods, particularly for those who have had severe illness. The Group considered that recuperation from COVID-19 infection impacts some people more than they would normally expect from other viral illnesses.

1.20. The Advisory Group considered that the impact of a potential reduction in symptoms on an individual's ability to return to paid employment or unpaid whānau and community responsibilities sooner after COVID-19 infection could have significant impact on themselves and their family and whānau. The Group noted the potential impact that unpaid sick leave for COVID-19 could have on family finances and people's quality of life in general. The Group noted that public health isolation measures of acute cases are intended to reduce the risk of transmission to protect people at high risk of severe disease. The Group considered that the current isolation measures for acute COVID-19 could disproportionately burden certain groups unable to get the appropriate level of support, financial or otherwise, and considered that there would still be benefit for some groups in getting back to paid employment sooner (in those cases when their illness extended beyond the 7-day mandatory isolation period). The Group also noted that such economic impacts were not considered in this analysis as they are not included in Pharmac's PFPA, for reasons explained in the PFPA.

1.21. The Advisory Group noted that the PANORAMIC study may provide more evidence to inform assumptions regarding long COVID.

Summary for assessment

1.22. The Advisory Group considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for the cost-effectiveness analysis of nirmatrelvir with ritonavir for symptomatic COVID-19. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Adults with acute COVID-19 (≤5 days from symptom onset) at high risk of progressing to severe disease For the purposes of the economic analysis, results are separately modelled for those aged 40-49, 59-59, 60-69 and 70+ years. Separate analysis also conducted for Māori and Pacific peoples due to greater risk of severe COVID-19 in these groups.
Intervention	Nirmatrelvir with ritonavir, 100mg twice daily for 5 days
Comparator(s)	No antiviral treatment; best supportive care
Outcome(s)	Reduction in risk of hospitalisation/death - Effectiveness modelled off more recent observational evidence, rather than EPIC-HR study, due to greater applicability to the New Zealand context - Relative risk reduction in hospitalisation/death likely to be greater and more certain for older populations and those at greater risk of severe COVID-19 Plausible but uncertain outcomes - Reduction in post-acute mortality (i.e. more than 28 days after infection) for those in older age groups Reduction in long Covid associated sequelae
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

2. High Risk Conditions

Application

2.1. The Advisory Group reviewed information relating to high-risk conditions for inclusion in the access criteria for community COVID-19 treatments.

2.2. The Advisory Group took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

2.3. Advisory Group **recommended** that the following groups be considered for inclusion in the access criteria, beyond the current existing criteria already:

- Pre-existing clinically severe frailty and/or likely high vulnerability due to severe or very advanced prior hospital-identified/based chronic comorbid disease, including but not limited to:
    - severe neurological conditions
    - severe cardiovascular conditions
    - severe renal conditions
    - severe respiratory conditions eg conditions that result in a low FEV1
- Pre-existing likely high vulnerability due to disability warranting direct family, whānau or external care most days

2.3.1. In making these recommendations, the Advisory Group considered that these were groups in addition to those already funded (eg. those aged 65+ years and Māori and Pacific peoples aged 50+ years).

2.4. The Advisory Group considered the following in making these recommendations:

- Antivirals reduce the risk of hospitalisation and warrant equitable distribution using a risk threshold.
- Risk of hospitalisation increases with increasing age (and presumed frailty), for those who have not been vaccinated, or for those with multiple comorbidities (≥2).
- Those at high risk of hospitalisation were considered to be at a risk of more than 5-10% of hospitalisation due to COVID-19 infection. However, the strength and quality of evidence for the risk of hospitalisation of specific conditions, in general, is weak.
- Certain groups of people feel concern that they are unable to access antiviral treatment despite feeling vulnerable to severe outcomes from COVID-19 infection.
- In general, more simple criteria are easier to understand and implement and are thus preferred.

2.5. The Advisory Group considered the following in making these recommendations, with respect to the specified groups:

- *Disability Support Services recipients*:
    - Available data were not sufficient to specify within the criteria
    - More information is expected to become available in coming months
- *People with rare disorders*:
    - Rare disorders as a single criterion is too broad and includes conditions that differ in likely hospitalisation risk from COVID-19 and would unnecessarily include who are likely not at risk.
    - Those at risk most likely have conditions impacting neurological, renal, cardiovascular or respiratory systems
- *People with severe respiratory conditions (asthma, bronchiectasis, COPD and cystic fibrosis)*:
    - Those with severe respiratory conditions are more likely to be at risk of hospitalisation from COVID-19 infection
    - Those with complications from cystic fibrosis, such as being underweight or pancreatic insufficiency, were likely at higher risk of hospitalisation, but this was likely to be similar risk to other people with other severe respiratory conditions eg asthma, bronchiectasis or COPD.
    - In general, those with severe neurological or cardiovascular conditions also were at similar risk to those with severe respiratory conditions

Discussion

Māori impact

2.6. The Advisory Group discussed the impact of COVID-19 antivirals for the treatment of COVID-19 on Māori. The Group noted its previous consideration of risk factors for hospitalisation or death from COVID-19 including age, vaccination status, number of comorbidities and ethnicity, specifically Māori. The Group considered that older people, those who have not received three doses of the vaccine, those with multiple comorbidities as listed by Ministry of Health, and Māori are at higher risk of severe COVID-19.

Background

2.7. The Advisory Group noted that, in general, reported COVID-19 cases in New Zealand are decreasing as well as hospitalisations associated with COVID-19 (Te Whatu Ora. COVID-19 in New Zealand. Updated 5 December 2022). The Group considered the composite immunity from COVID-19 infection and vaccination may wane over time and offer less protection against hospitalisation and symptomatic disease. The Group considered that for most of the population the current risk of hospitalisation (<1-2%), ICU and death from COVID-19 infection is presently low, particularly for people who are well vaccinated (≥3 doses), not elderly (eg <70 years), unless they have other substantial risk factors.

2.8. The Advisory Group noted that Pharmac had received requests from several groups requesting that the access criteria for COVID-19 antivirals be widened, to explicitly include people with cystic fibrosis, people receiving disability support services, and people with a rare disorder, and to consider the impact of COVID-19 reinfection and long COVID-19. Specifically, the Group was asked to consider these clinical settings:

2.8.1. People with multiple COVID-19 infections

2.8.2. Disability Support Services recipients

2.8.3. People with rare disorders

2.8.4. People with particular respiratory conditions (asthma, bronchiectasis, COPD, cystic fibrosis)

2.8.5. People with any prior hospital identified/based comorbid condition(s)

2.8.6. People previously hospitalised due to COVID-19

2.8.7. People with long covid or post-acute sequelae of SARS-CoV-2 infection (PASC)

Current access criteria

2.9. The Advisory Group considered that the current access criteria for COVID-19 antivirals had been designed to provide access to COVID-19 antiviral treatment to people with the highest risk of hospitalisation from COVID-19 infection (previously estimated as a 10% risk of hospitalisation). The Group noted that the access criteria was intended to provide access to people with this risk of hospitalisation regardless of the cause. The Group considered that rationale for this was/is in part because the main clinical trials providing

evidence for the effectiveness of COVID-19 antivirals had hospitalisation and mortality as their principal outcomes in participants who were at high risk of these COVID-19 related outcomes due to specified medical conditions.

2.10. The Advisory Group noted that the current access criteria for COVID-19 antiviral treatments include age, vaccination status ethnicity and counts of specific comorbidities, but do not currently allow for factors such as the severity of prior COVID-19 infection, the severity of existing comorbidities or disability, or a person's socioeconomic deprivation.

2.11. The Advisory Group noted its previous consideration of risk factors for hospitalisation or death from COVID-19 including age, vaccination status, number of comorbidities and ethnicity, specifically Māori and Pacific peoples. The Group considered that older people, those who have not received three doses of the vaccine, those with multiple comorbidities as listed by Ministry of Health, and Māori and Pacific peoples are at higher risk of severe COVID-19.

2.12. The Group considered those people with a single severe comorbidity, those living with a disability, those experiencing socioeconomic deprivation, and the severity of current COVID-19 infection. The Group considered the level of socioeconomic deprivation could affect outcomes from COVID-19 infection but would be difficult to assess in clinical practice, disentangle from other confounding factors and implement within the criteria. The Group considered that using the potential severity of current COVID-19 illness would be difficult to implement, as early treatment with antivirals is required in the first five days of symptoms, ideally as early as possible after diagnosis.

Health need

2.13. The Advisory Group was informed of data collected by a member of the Advisory Group, from two Wellington PHOs of 126,000 COVID-19 cases, which included data on chronic comorbidities. The Group noted case hospitalisation rates indicated the risk of hospitalisation was most significant in those 70 years and over. The Group noted that about half of the cases flagged as hospitalised were assessed and discharged from emergency departments (ie did not require admission to an inpatient ward). The Group noted that removing emergency department data meant the majority of hospitalised COVID-19 cases were children admitted to paediatric wards, women 20-35 years admitted to women's health wards, and the largest group was adults (aged 40 years onwards) admitted to medical wards, with peak age of admission in those 70-79 years. The Group considered that the admissions to women's health wards were most likely due to pregnancy and not due to chronic morbidities comorbidities.

2.14. The Advisory Group considered comorbidity-related data suggested that in people hospitalised for COVID-19, as age increased so did the number of comorbidities that they had upon admission, where the majority of people under 50 years had no comorbidities when presenting to hospital, whereas the majority of people aged 70-79 years had one or more comorbidities. Of the comorbidities categorised from the PHO supplied data, the Group noted that the univariate analysis suggested that those with lung, cardiac or renal conditions had higher risks of hospitalisation compared to those with conditions affecting other systems such as neurological, mental health, or specific groups such as people living with cancer, diabetes or hypertension.

2.15. The Advisory Group noted that much of the data presented and available regarding COVID-19 infection has been univariate analysis. The Group considered that the many risk factors have overlap or interaction within individuals. The Group considered that a multivariate analysis would be more appropriate to assess the risk associated with each factor with less confounding from other factors.

2.16. The Advisory Group considered the application of this information and the risk of each group when considering factors known to influence the risk of severe COVID-19 requiring hospitalisation such as vaccination status, comorbidities, age, and inequities between ethnic groups in New Zealand. The Group noted that the current Omicron variant(s) case less severe disease than previous circulating variants of COVID-19. The Group considered that the current criteria were likely allowing for wider access than the 5-10% risk of hospitalisation that was originally intended by the access criteria. The Group considered that if not adjusting for vaccination status or ethnicity, those aged over 70 years or anyone with two or more comorbidities were likely to be at high risk of hospitalisation from COVID-19 infection with the current Omicron variants.

2.17. The Advisory Group considered that comparison to the average risk of hospitalisation or death associated with COVID-19 for the general population includes people who could have a significantly higher risk or lower risk depending on a number of factors. The Group considered that a person with a condition(s) associated with an increased relative risk of hospitalisation or death of those with any specified risk factor compared to the general population may still have a risk of hospitalisation lower than 5%, if the risk in the general population has diminished (eg due to Omicron and/or vaccination).

2.18. The Advisory Group considered the lower risk of hospitalisation and severe COVID-19 in the general population with Omicron infection compared to previously circulating variants of SARS-CoV-2. The Group considered that other factors involved in the choice whether to widen access to oral antivirals included drug interactions, adverse effects, potential drug resistance, and health workforce capacity to implement the funding changes.

2.19. The Advisory Group considered that hospitalisation related to COVID-19 infection in New Zealand is associated with age, with risk increasing meaningfully in those aged over 60 years and with a considerable increase in risk in those over 70 years. The Group considered that the COVID-19 deaths are largely in the older age groups (>80 years) and decrease as ages decreases. The Group considered the risk of hospitalisation is increased in those that are unvaccinated or insufficiently vaccinated (received less than 3 doses as a 2+ primary course and subsequent 1 booster) compared to those that are fully on-time vaccinated.

2.20. The Advisory Group considered that those people with single comorbidities, regardless of severity (including prior hospital-identified/based conditions), have a much lower risk of developing severe COVID-19, but when comorbidities are considered in combination there is a higher risk of severe COVID-19.

COVID-19 reinfection

2.21. The Advisory Group considered that overall, there was likely to be a similar health need from an initial infection compared to sequent infections. The Advisory Group noted a number of studies that reported variable impact after COVID-19 re-infection, including:

- Bowe et al. Nat Med. 2022; 28(11): 2398-405
  This study using data from US Veterans Affairs database reported that, compared with no reinfection, reinfection contributed additional risks of death (hazard ratio (HR) = 2.17, 95% CI, 1.93–2.45), hospitalisation (HR = 3.32, 95% CI 3.13–3.51) and clinical sequelae including pulmonary, cardiovascular, haematological, diabetes, gastrointestinal, kidney, mental health, musculoskeletal and neurological disorders. The risks were evident regardless of vaccination status.
- Brouqui et al. Eur J Clin Invest. 2021; 51(5): e13537
  This French study reported that of 46 patients, 27.8% had more severe disease in the second episode, with 8.1% admitted in ICU or dying, 29.5% had less severe subsequent disease, and 42.6% presented the same severity for both episodes. However, only the difference in those presenting with mild to moderate symptoms was statistically significant (94.8% v 78.7% *P*= 0.044), with more severe presentations not statistically significant (*P* >0.05), possibly reflecting underpowering with small numbers.
- Nguyen et al. Emerg Microbes Infect. 2022; 11(1): 894–901
  This French study on the risk of re-infection in 55,338 cases of COVID-19, and the severity of these infections in the 209 reinfected patients identified, reported no difference in severity between the first infection and subsequent re-infections (defined as an infection >90 days after initial infection).

2.22. The Advisory Group noted that the majority of people currently being hospitalised as a result of COVID-19 would already be at least eligible to access antiviral treatments via the current access criteria.

People receiving disability support services

2.23. The Advisory Group noted that disability support services recipients are a small subgroup of all disabled New Zealanders, who are substantially more likely to be highly vulnerable with complex impairments. The Group noted that in 2018 there was 38,342 people accessing disability support services (Ministry of Health. 2019. Demographic Report for Clients Allocated the Ministry of Health's Disability Support Services: 2018 update). The Group noted that those accessing this funding are mainly under 65 years and need ongoing support to live independently, to the extent that ongoing support is required, or with developmental, physical, intellectual or sensory disabilities or neurological conditions that result in a disability (Ministry of Health. 2019).

2.24. The Advisory Group noted that some disabled people could access antivirals under the current criteria for those with underlying medical conditions. The Group considered that defining who is disabled can be difficult. Globally disabled people are recognised as a vulnerable group who are likely to be at higher risk of contracting COVID-19 and experiencing severe COVID-19 related health outcomes.

2.25. The Advisory Group considered that those living with neurological disabilities had some evidence to suggest there is an increased risk of death or hospitalisation related to COVID-19, in particularly for those with Down syndrome. The Group considered that

other conditions lacked clear evidence to support an increased risk of death related to COVID-19.

2.26. The Advisory Group noted that Whaikaha – Ministry of Disabled People expected to publish soon a review of data regarding the impact of COVID-19 infection for disabled people including tāngata whaikaha Māori. The Advisory Group considered this information would be helpful for it to consider changes to the access criteria to meet the needs of disabled people.

People with a rare disorder

2.27. The Advisory Group considered that rare disorders cover a large group of conditions that often affect more than one organ system. The Group considered that the rarity of these conditions made the assessment of evidence reporting the severity and impact of COVID-19 infection difficult. The Group considered that multiple organ systems may be affected with different severity and dysfunction resulting in at times significant health challenges.

2.28. The Advisory Group noted the results of a literature search conducted by Pharmac staff including the following:

- Zhang et al. Orphanet J Rare Dis. 2022;17:166
  Participants with rare disorders who tested positive for SARS-CoV-2 in the Genomics England 100k Genomes projects had increased risk of COVID-19 related death compared to their unaffected relatives during the first wave of the pandemic in UK, although the increase was not significant after accounting for age and numbers of COVID-19 related comorbidities. An increased risk of COVID-19 related death was reported in those with pre-existing neurology and neurodevelopment disorders in both univariable and multivariable analysis. It was reported that overall, for those over 60 years had a higher risk of mortality (adjusted odds ratio (aOR) 9.95 (95% CI, 3.52, 28.17)) when adjusted for having at least 2 comorbidities expected to increase risk of COVID-19 related mortality and being affected by rare diseases.
- Boudjelal et al. J Infect Dev Ctries 2021;15:450-62
  The effects of COVID-19 potentially worsen rare disease related conditions due to several factors, including cytokine storm, cardiovascular damage or failure and neurological effects. In addition, those living with intellectual disability face potential challenges in managing a COVID-19 infection. Recommendations for the treatment of these patients include care for those with COVID-19 to align with current COVID-19 guidelines, education and psychological support to prevent a worsening of overall morbidity or mortality.

2.29. The Advisory Group also considered studies related to inherited metabolic disease (Paneghetti et al. Orphanet J Rare Dis. 2022;17:109P), Gaucher disease (Fierro et al. Mol Genet Metab. 2021;132:44-8), alpha 1-antitrysin deficiency (Ferrarotti et al. Respir Med. 2021;183:106440) and amyloidosis (Lewis et al. Ann Hematol. 2022;101:2307-15).

2.29.1. The Group considered that overall the outcomes for these specific indications differed depending on the condition. The Group noted in particular that those with

alpha-1 trypsin deficiency were reported to be more susceptible to infection, but mortality related to COVID-19 was not higher than the general population (Ferrarotti et al 2021).

2.30. The Advisory Group further noted the following studies relating to the impact of COVID-19 on people with rare disorders:

2.30.1. Chowdhury et al. Front. Public Health. 2021;9:640282

2.30.2. Karca et al. Orphnet J Rare Dis. 2022;17:338

2.31. The Advisory Group acknowledged correspondence from Rare Disorders NZ raising concerns that many people with rare disorders in New Zealand are unable to access COVID-19 antivirals because they do not meet the current criteria, despite having a similar health risk to eligible populations. The Group noted an additional letter from Genetic Health Service New Zealand requesting access to antiviral treatments for people with intellectual disabilities.

2.32. The Advisory Group considered that the large group of conditions that may be considered rare disorders makes the assessment of the impact of COVID-19 difficult and challenging to incorporate into the access criteria for antiviral treatments. The Group considered it was important to recognise that some rare disorders would increase a person's risk of severe illness from COVID-19 while others would not.

2.33. The Advisory Group considered that people with rare disorders that impact neurological function, such as swallowing, or impact respiratory function, could be harmed more by COVID-19 than people with conditions affecting other organ systems.

2.34. The Advisory Group considered that people with rare disorders or disabled people face important health challenges over their lifespan and in their daily lives. The Group acknowledged that this may result in the feeling that this was inequitable for people with these conditions compared to other groups who are currently able to access COVID-19 antiviral treatments. The Group also acknowledged the significant responsibility for those that care for people living with these, often, lifelong and debilitating conditions and the potential impact of COVID-19 on their carers.

People with particular respiratory conditions

2.35. The Advisory Group considered that people with certain respiratory conditions (in particular asthma, bronchiectasis, COPD, cystic fibrosis) are likely to be more susceptible to COVID-19 infection than other people, but this did not necessarily result in these people being more likely to experience severe COVID-19. The Group considered that the severity of the respiratory condition likely relates to the risk of severe COVID-19 and therefore hospitalisation.

2.36. The Advisory Group considered that the evidence varied in design and reported conflicting results (Sunjaya et al. Eur Respir J. 2022;59:2101209; Gerayeli et al. EClinicalMedicine. 2021;33:100789). The Group noted that a number of the studies were observational studies of lower strength or quality. The Group considered that those with the same condition, but more severe presentations are more likely to experience severe outcomes from COVID-19.

2.37. The Advisory Group considered that although the research literature on the impact of the severity of conditions on COVID-19 outcomes (mortality or hospitalisation) is limited, there are data to support more severe presentations of a condition having worse mortality and hospitalisation outcomes.

2.38. The Advisory Group considered that for those with severe asthma or severe cystic fibrosis (low FEV1, pancreatic insufficiency or being underweight) there was an increased risk of severe COVID-19.

2.39. The Advisory Group noted its previous consideration (October 2022) for the inclusion of cystic fibrosis for funding of oral antivirals, and considered that the risk for those with cystic fibrosis was likely to be similar to other severe respiratory conditions.

Health benefit

2.40. The Advisory Group noted the previously considered randomised, placebo-controlled trials for currently funded COVID-19 antivirals (molnupiravir, nirmatrelvir with ritonavir and remdesivir), noting the primary outcomes in all trials were hospitalisation or death, as follows:

- molnupiravir: Bernal et al. N Engl J Med. 2022;386:509-20
- nirmatrelvir with ritonavir: Hammond et al. N Engl J Med. 2022;386:1397-408
- remdesivir: Gottlieb et al. N Engl J Med. 2022;386:305-15

2.41. The Advisory Group considered there was no specific evidence relating to the benefit (reduction in hospitalisations or mortality) in the groups considered above. The Group considered that the benefit of currently funded COVID-19 antivirals in those with a similar risk of severe COVID-19 (resulting in hospitalisation or death) would be the same for those being considered for funding.

Proposed changes to access criteria

2.42. The Advisory Group considered that the current access criteria were broad and considered that, in general, evidence to support the inclusion of the requested additional conditions specifically was lacking. The Group was not supportive of making the criteria more complex, as previous attempts to implement prescription of treatments with very complex criteria had been associated with uptake rates much lower than expected.

2.43. The Advisory Group acknowledged that some people felt particularly vulnerable to severe COVID-19 and that the current criteria did not allow them access to treatment. The Group considered the lack of supportive data relating to risk of COVID-19 for particular comorbidities, regardless of the interplay of other risk factors (some accessing treatment already), made it difficult to assess the benefit in these groups and the potential adverse effects that they may experience.

2.44. Based on its discussion and consideration of available evidence, the Group was supportive of the following changes being made to the access criteria:

- Including, as a specific named group, those people who are considered clinically to have severe frailty, which the Group considered would likely encompass those

people at highest risk of COVID-19 without needing to produce an exhaustive list of specific high-risk conditions.

- Including, as a specific named group, those people with severe disability either needing direct family, whānau or external care most days.
- An increase in some of the age limits (ie narrowing of access), with all people aged 70 years old and over and Māori and Pacific peoples 60 years and over being eligible without any additional restrictions.

2.45. The Advisory Group considered that any changes to some of the age limits, with the funding of COVID-19 antivirals for people aged over 70 years and for Māori and Pacific peoples aged over 60 years would be more restrictive than the current criteria (currently ages 65+ and 50+ respectively). The Group considered that those aged 65-70 years and Māori and Pacific peoples aged 50-60 years without other risk factors, especially if vaccinated, may no longer be at high risk of hospitalisation. No change was recommended to the eligible ages for people who had not received the three doses of COVID-19 vaccine (ie remaining at age 50+ years without any additional restrictions).

2.46. The Advisory Group considered it would be helpful for Pharmac to engage with affected groups over the specific wording of the criteria, including Whaikaha - Ministry of Disabled People, to accurately define these groups.

Review of molnupiravir access

Application

4.1. The Advisory Group reviewed the evidence supporting access to molnupiravir.

4.2. The Advisory Group took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

4.3. The Advisory Group **recommended** that funding of molnupiravir be discontinued.

4.4. The Advisory Group considered the following in making this recommendation:

- The Group considered there to be no credible evidence that molnupiravir, in New Zealand's highly vaccinated population in the current SARS-CoV-2 Omicron variant(s) era, prevents hospitalisation or death in any cohort of high-risk patients, including people who are immunocompromised or immunosuppressed (such as people with solid organ transplants).
- There is some evidence that the speed of recovery following COVID-19 infection may be quicker in those treated with molnupiravir but that the quality of life (QoL) benefit of this effect is, as yet, unquantified (QoL data are awaited).
- The ongoing use of molnupiravir in high-risk groups, such as the immunocompromised, older people or Māori and Pacific peoples with mild to moderate COVID-19 infection, appeared unjustifiable, given the present data.

Discussion

Māori impact

4.5. The Advisory Group discussed the impact of funding molnupiravir for the treatment of COVID-19 on Māori health areas of focus and Māori health outcomes. The Group noted the use of molnupiravir was higher in Māori and Pacific peoples' cases of COVID-19 than non-Māori, non-Pacific peoples' cases across all age groups. The Group considered the use in Māori and Pacific peoples appeared inequitable. The Group noted that the presented data did not account for the concurrent use of medicines that may interact with alternative antiviral options, rendering molnupiravir the only oral option. The Group noted that this confounding was not quantifiable in any group for the presented data.

Background

4.6. The Advisory Group has previously considered evidence for molnupiravir on a number of occasions, in particular:

4.7. In October 2021, the Group considered unpublished MOVe-IN and MOVe-OUT randomised placebo-controlled trials (RCTs) and other clinical evidence for molnupiravir in mild-moderate COVID-19, recommending molnupiravir be funded, subject to Medsafe approval, for the treatment of mild to moderate COVID-19, subject to access criteria.

4.8. In February 2022, the Group noted the previous molnupiravir criteria recommendations made in October 2021 were made prior to the availability of full data, including the exclusion criteria, for the clinical trial. Members noted that further relevant information now available was that the trial's eligibility criteria excluded vaccinated individuals. The Group considered, in effect, that the access criteria for nirmatrelvir with ritonavir, molnupiravir and remdesivir should be harmonised,

updating recommended access criteria for molnupiravir to align with those of nirmatrelvir with ritonavir as the other oral antiviral COVID-19 treatment. The Group noted that as evidence continued to evolve, further consideration of the access criteria may be required.

4.9. In August 2022, the Group considered evidence from three unpublished cohort studies provided by the supplier, but deferred any recommendations until further data was available.

4.10. In October 2022, the Group considered a pre-print of the PANORAMIC trial and recommended that, based on the information available, nirmatrelvir with ritonavir (Paxlovid) or remdesivir be the preferred antiviral treatments for people with COVID-19, and molnupiravir only be considered when both nirmatrelvir with ritonavir or remdesivir are not accessible or are clearly clinically inappropriate.

Health benefit

4.11. The Advisory Group noted the evidence for benefit of molnupiravir for the treatment of mild to moderate COVID-19, both that evidence considered in October 2021 but also with the following new considerations:

4.12. The Group considered again the phase III MOVe-OUT randomised controlled trial, in the form of the final all-randomised results as published online in December 2021 (Bernal et al. N Engl J Med. 2022;386:509-20). This updated the earlier results from the prespecified interim analysis for early efficacy or futility from 5 October 2021 (ClinicalTrials.gov NCT04575597) and considered by the Advisory Group on 21 October 2021.

4.12.1. The Group noted it had considered MOVe-OUT was the pivotal trial in an unvaccinated population, with Delta variant being the predominantly circulating variant in the study's source population at the time (COVID-19 cases from May to October 2021 from 20 countries worldwide but not Australasian or Pacific Island nations), with Alpha, Beta, Gamma and Mu variants also in circulation. The Group reiterated that the trial excluded vaccinated people.

4.12.2. The Group noted that those people included in the trial were considered to be at high risk of severe COVID-19.

4.12.3. The Group noted the statistically significant decrease in combined hospitalisation and death; of all 1433 participants who had been randomised, 6.8% of the molnupiravir group were hospitalised or died through day 29 [48 of 709] compared with 9.7% in the placebo group [68 of 699]; difference -3.0% (95% CI -5.9% to -0.1%); hazard ratio (HR) 0.69 (95% CI 0.48 to 1.01). The Group noted this 31% relative reduction in event rates was appreciably less than the 50% risk reduction reported earlier in the 5 October 2020 interim analysis (ClinicalTrials.gov NCT04575597).

4.12.4. The Group considered the final absolute reduction to be both small and imprecise with statistical significance that was borderline, with the difference's 95% upper confidence limit almost breaching 0%, vulnerable to very small numbers of misclassified outcomes being able overturn the statistical significance of the finding.

4.13. The Group considered a subgroup analysis of those included in MOVe-OUT who were immunocompromised (55 participants, ie. 4% of total trial participants) randomised to molnupiravir treatment or placebo groups (Johnson et al. Infection. [Epub ahead of print] 2023:1-12). The Group noted that most immunocompromised participants had cancer, some had immunosuppressive therapy and five were transplant recipients; their median age was 49 years, compared with 42 years for MOVe-OUT's 1163 non-immunocompromised participants for those treated with

molnupiravir. The Group noted that fewer immunocompromised participants were hospitalised or died through Day 29 in the molnupiravir group. The Group noted that days 1-29 cumulative combined all-cause incidence of hospitalisation or death was 8.3% [2/24] compared with 22.6% [7/31] in the placebo group, but that the -14.2% absolute difference was not statistically significant (95% CI -33.5% to +6.6%). The Group also considered that the reported reduction in death alone was not statistically significant. The Group noted the reported reduction in the viral load in the molnupiravir treatment group meant that there was a reduction in the response detected in convalescent sera in these patients.

4.14. The Group noted the higher proportion (5.5% ([3/55]) of MOVe-OUT immunocompromised participants dying compared with non-immunocompromised participants (0.5% [7/1353]), and considered this 10-times higher mortality with immunocompromise and the 5.5% absolute mortality rate indicated high unmet need.

4.15. The Group noted its previous consideration of unpublished results from the PANORAMIC study and the study's results' recent publication (Butler et al. 2023; 401(10373):281-93).

4.15.1. The Group considered the predominant Omicron variant and vaccinated population (>90% population with 3 for more doses) directly related to the New Zealand COVID-19 response, vaccination rates and circulating variant(s).

4.15.2. The Group noted the sub-group analysis reported the immunocompromised patients (9% of the total study population) had an odds ratio of 1.89 favouring usual care, however this was not statistically significant (95% CI 0.99 to 3.73).

4.15.3. The Group considered the reported benefit of reduction in GP visits and fewer home hospital visits, but the quality of life benefit from this was unclear.

4.15.4. The Group noted that there is EQ-5D quality of life data that is yet to be released by the PANORAMIC investigators. The Group considered that without quality of life data to quantify a clear benefit, the cost of GP visits or home hospital visits would have little impact against the cost of molnupiravir.

4.15.5. The Group considered there was no evidence of changes in viral genome because of the use of molnupiravir. The Group considered that this would have been observed given the large scale of the study.

4.16. The Advisory Group considered evidence for the use of molnupiravir in people with renal transplants:

4.16.1. The Group noted an observational study in 122 people with renal transplants (Radcliffe et al. Am J Transplant. 2022;22(10):2458-63). The Group considered that no statistically significant improvement in hospital or death with molnupiravir (n=49) (*P*>0.05) based on a Fischer exact test performed by Members.

4.16.2. The Group considered an unpublished, observational study from the United Kingdom in the Omicron BA.1 variant era that considered 142 people who had received kidney transplants and the efficacy of sotrovimab, molnupiravir or no treatment (Gleeson et al. Preprint 2022). The Group noted that the authors reported no evident reductions in post-diagnosis dialysis, ICU admission or death in those who were treated with molnupiravir.

4.16.3. The Group considered a cohort study from Spain of 9 participants treated with molnupiravir and 7 treated with remdesivir (Villamarín et al. Transplantation. 2022;106(11):2200-4). The Group noted this study was conducted in the Omicron variant era and all participants were vaccinated. The Group noted that no remdesivir-treated participants progressed in COVID-19 severity, but one

molnupiravir treated participant did progress to pneumonia requiring hospitalisation, but that the study was small, observational and had differing baseline characteristics between the few participants.

4.17. The Advisory Group considered that molnupiravir was a safe treatment, however there was no additional benefit for the use of molnupiravir in those with renal transplants or in other immunosuppressed people. The Group considered these recent Omicron-era data complemented the RCT and large observational studies in concluding there to be little clinical value in the use of molnupiravir.

4.18. The Group further considered the applicability of the PANORAMIC study and other earlier RCT evidence to the New Zealand setting including high risk populations.

4.18.1. Members noted people with very high risk were excluded from PANORAMIC, and that this constraint meant few people aged 80 years and over participated (n=527, 2% of 25708 all ages),

4.18.2. Members noted that the trends toward risk reduction for hospitalisations or death in the PANORAMIC study for those aged 65 years and over and those aged 80+ years were not statistically significant, although commenting that low numbers of participants in those age groups would have affected the trial's ability to detect statistically significant differences.

4.18.3. Members also observed that the final results of MOVe-OUT (Bernal et al. 2022) suggested molnupiravir may have much less effect on hospitalisation or deaths in older people than had been signalled in MOVe-OUT's interim results considered by the Group in October 2021.

4.18.3.1. Members recalled the MOVe-OUT interim results for those aged over 60 years had been encouraging, with the reported 3.6% hospitalisation rate in molnupiravir participants compared with 21.4% in placebo participants (implied RR 0.17).

4.18.3.2. Members however observed, now, that those early signals of effect did not eventuate in the final all-randomised MOVe-OUT analysis (Bernal et al. 2022). Instead, Members considered the situation had reversed, that the final analysis signalled that molnupiravir was clearly not more effective in those aged over 60 years. In the final analysis, for those aged >60, 10.2% of molnupiravir participants were hospitalised or died by day 29 compared with 12.7% in the placebo group, difference -2.4% (95% CI -10.6% to +5.8%), implied RR 0.81 (12/118 vs 16/127). This compared with the final results' RR of 0.70 overall, difference -3.0% (95% CI -5.9% to -0.1%).

4.18.3.3. Although acknowledging older people had a relatively low prevalence in MOVe-OUT (245/1408 were aged over 60 years, ie. 17.4% of participants), Members considered that not only was the final reduction in hospitalisation or death for those aged over 60 years not statistically significant, but the effect size was less than for all patients overall. Members considered that the final effect (RR 0.81, ie a 19% relative risk reduction) was markedly less than the interim analysis' result (RR 0.17, ie an 83% reduction).

4.19. The Advisory Group considered that there was no subgroup of people with any health condition or particular heath need who would benefit from using molnupiravir. The Group considered that if molnupiravir was to be delisted from the Pharmaceutical Schedule then there would be no express subgroup negatively affected. The Group considered that those people unable to eliminate the virus may

have some use for molnupiravir due to the reduction in viral load observed in the MOVe-OUT studies, however this use was without clinical evidence.

4.20. The Advisory Group noted the current pattern of use of molnupiravir, specifically that the proportion of use relative to other antivirals has not changed since the time of listing. The Group considered that previous changes to access criteria via footnotes, to reduce molnupiravir use in favour of other antivirals, had not been effective, and that a more explicit change would likely be required to change dispensing behaviour.

4.21. The Advisory Group noted the use of molnupiravir was higher in Māori and Pacific peoples than non-Māori, non-Pacific peoples across all age groups. The Group considered the that the use in Māori and Pacific peoples was inequitable. The Group noted that the presented data did not account for use of medicines that may interact with alternative antiviral options and thus contraindicate use of those alternatives, rendering molnupiravir the only oral option. The Group noted that this confounding was not quantifiable in any group for the presented data.

4.22. The Advisory Group noted that there is a small group of people for whom changing their usual treatment regimens to manage drug interactions with nirmatrelvir with ritonavir would be particularly difficult, such as those whose medicines are blister packed.

4.23. The Advisory Group considered that, although listing on the Pharmaceutical Schedule did not indicate that a particular treatment is efficacious or how it should be used in clinical practice, given the emergency response phase that COVID-19 treatments were funded in and the comprehensive access criteria, there may be an assumption that listed treatments are efficacious. The Group considered the continued listing of molnupiravir could inadvertently prevent the use of other antivirals that are probably more effective in reducing hospitalisation.

4.24. The Advisory Group considered that the basic infection prevention measures such as mask-use, hand-washing, social distancing, good indoor ventilation/airflow, case self-isolation etc. have prime importance in the primary prevention of transmission of COVID-19, and that vaccination is the most important intervention for reducing severity of disease. The Group also considered that prescription of other treatments such as simple analgesics or electrolytes are also helpful in recovering from any viral illness.