Record of the COVID Treatments Advisory Group Meeting held on 31 October 2022

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
Eamon Duffy
Dr Gillian Hood
Dr Graham Mills
Dr Justin Travers
Dr Marius Rademaker
Dr Nigel Raymond
Professor Stephen Munn

Apologies
Professor Brian Anderson
Dr Jessica Keepa
Dr Kerry Benson-Cooper
Dr Robyn Manuel
Dr Tim Cutfield

1. Pharmac Update

Application

1.1. The Advisory Group reviewed the update of information for COVID-19 Treatments.

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 noted the antiviral access criteria changes that were made partly because feedback suggested the criteria were complicated and difficult to interpret. The Group noted this complexity was concerning as it is a potential barrier to eligible groups, in particular Māori. The Group considered the ethnicity criteria likely to be targeting the correct people but were unable to consider the accessibility of treatments, particularly for rural Māori, based on current dispensing data provided to the Group being limited to district, age and ethnicity (not rurality). The Group noted the recent extension of funded treatment access to all Māori cases 50 years and over. The Group noted the rate of use of molnupiravir in older people and Māori to be higher than in younger age groups and in other ethnicities. The Group considered that the perception that molnupiravir is safer and easier to prescribe could result in increased prescribing.

COVID-19 Trends

1.5. The Advisory Group noted the current case numbers for COVID-19 as reported by region and age to be similar to previous reporting. The Group noted that the proportion of Omicron BA.5 subvariant circulating was estimated to be 84% with BA.2, BA.2.75, BA.4 and BA.4.6 making up the other 15% of circulating cases, at the time of meeting.

1.6. The Advisory Group noted the trend for daily hospital admissions for COVID-19 and daily mortality had decreased since July to mid-September but was beginning to increase in October. The Group noted that this was expected to increase into December, assuming the same variants are still circulating, waning vaccine immunity and relaxing of public health behaviours (masking, social distancing etc.). The Group noted that the proportion of cases that were subsequent infections was still small but would likely increase over time.

Community-based oral antivirals (nirmatrelvir with ritonavir (Paxlovid) and molnupiravir)

1.7. The Advisory Group noted the extension of access to oral antivirals to all the following groups of people:

- aged 65 years and over
- Māori and Pacific peoples aged 50 years and over
- aged 50 years and over who have not received a primary vaccination course
- not eligible under the above age criteria but having at least three comorbidities as listed on the Ministry of Health website.

1.8. The Advisory Group noted people in critical or high dependency care were added to criterion 4.4 in addition to ICU care for those being treated in hospital.

1.9. The Advisory Group noted that the 14 September 2022 changes to the access criteria were expected to extend the eligible group from an estimated 10% of total cases to 24%. The Group noted that COVID-19 case numbers in New Zealand have remained relatively stable over the past few months while dispensing has increased since the widening of access. The Group noted the antiviral access criteria changes that were made partly because of feedback that the criteria were complicated and difficult to interpret and thus chanced cases at high risk not receiving treatment. The Group noted this feedback was concerning as it is a potential barrier to the eligible groups receiving treatment, in particular Māori and Pacific peoples who already experience the New Zealand health system unable to engage with them adequately.

1.10. The Advisory Group noted that the uptake of oral antivirals has increased with the extended access criteria and the proportion of dispensing for European/other and Māori and Pacific peoples have remained stable. The Group noted that for counts of total dispensing there was a steep increase from age 65 years, peaking at 75 to 79 years then declining thereafter in older age groups. The Group noted that the larger Te Whatu Ora districts had higher counts for total dispensing in Auckland, Canterbury, Southern, Waikato and Waitemata districts, aligning with those districts' larger populations, but that further interpretation was difficult as standardised case incidence and eligibility-adjusted dispensing rates were not available. The Group considered the access criteria for the antivirals to potentially be too wide.

1.10.1. The Group considered the benefit of these treatments in Māori and Pacific peoples under 50 years old and others under 65 years old to be low. The Group considered the inclusion of ethnicity in the criteria to be targeting people whose clinical circumstances were the most appropriate, but did not have sufficient information to comment on the accessibility of treatments for all groups, particularly for rural Māori. The Group considered the stratification of data by Te Whatu Ora district, ethnicity and age could give better insight into this.

1.11. The Advisory Group noted the rate of use of molnupiravir in cases who were elderly or Māori or Pacific peoples to be higher than cases in other groups. The Group considered that the perception that molnupiravir is safer and easier to prescribe due to much fewer drug/drug interactions when compared to nirmatrelvir with ritonavir could result in increased prescribing in elderly. In light of the expected lessened efficacy of molnupiravir compared to nirmatrelvir with ritonavir the Group considered the potential of post code prescribing at a practice level and considered that targeted education would be beneficial for Healthcare Professionals who appear to be over-prescribing molnupiravir.

1.12. The Advisory Group noted data of remdesivir stock ordering by Te Whatu Ora Hospital since January 2022. The Advisory Group noted that the Auckland district is the highest user of remdesivir and considered that the increased ordering reflects the changes in case numbers. The Group considered a change in the WHO guidelines to include a conditional recommendation for the use of remdesivir in severe COVID-19 and a conditional recommendation against the use of remdesivir in critical COVID-19. The Group considered that no change was required to the access criteria for use of for people with severe COVID-19 in hospital.

Tixagevimab with cilgavimab (Evusheld)

1.13. The Advisory Group noted data presented as to the dispensing of tixagevimab with cilgavimab stratified by Te Whatu Ora districts, but considered this to be incorrect as it appeared that some data were missing, and consequently were unable to comment further. The Group noted that in some cases this may be due to manual data collection.

1.14. The Advisory Group considered that it was likely that many of the people with a particularly high risk of severe outcomes from COVID-19 such as transplant patients and people under the care of renal services or rheumatology services had received tixagevimab with cilgavimab for the pre-exposure prophylaxis of COVID-19 in the initial early release of treatment.

1.15. The Advisory Group noted that a noteworthy volume of tixagevimab with cilgavimab stock was remaining and considered the likelihood of ongoing delivery of this treatment to be low, particularly in the services that had been less affected by severe COVID-19 outcomes or those services with less resource to identify eligible people and administer an additional intravenous therapy.

1.16. The Advisory Group also considered the criteria could be too wide and the risk profile across the eligible conditions could be considered similar, making it difficult to prioritise people with particular conditions within services. The Group considered that the unknown efficacy against emerging variants could also be a barrier to the delivery of this service.

1.17. The Advisory Group noted that the majority of the available stock is due to expire on 31 December 2022. The Group considered this could place services under additional time pressure to administer the therapy.

1.18. The Advisory Group considered that within secondary care services it was unlikely there would be an increase in the number of patients administered tixagevimab with cilgavimab. The Group considered the addition of administration in primary care in early October 2022 to be beneficial but unlikely to result in any major increased uptake. The Group did consider that some provincial and smaller centres were beginning to consider the use of this therapy for eligible people in their care but the impact of this was unclear.

Casirivimab with imdevimab and sotrovimab

1.19. The Advisory Group considered the efficacy of casirivimab with imdevimab and sotrovimab against currently predominant strains/variants of the SARS-CoV-2 to be too low to be recommended for empirical treatment, but considered that casirivimab with imdevimab should be reserved for those infected with a sensitive variant. The Group considered this would likely be a very small group of people.

1.20. The Advisory Group noted the current hold on Medsafe approval for sotrovimab in the treatment of COVID-19, and evidence the Group had previously reviewed that suggested low efficacy against currently circulating Omicron subvariants, and considered that sotrovimab was unlikely to be useful for the treatment of COVID-19 in New Zealand.

Horizon scanning

1.21. The Advisory Group noted other COVID-19 treatments not currently funded in New Zealand. The Group considered that some agents could be of value in the treatment of COVID-19 but the Group would require further information before recommending agents for funding.

2. COVID-19 treatments for people with Cystic Fibrosis (CF)

Application

2.1. The Advisory Group reviewed the application for COVID-19 treatments for those with CF.

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

Recommendations

2.3. The Advisory Group **deferred its recommendation** on the addition of CF to antiviral access criteria until issues of severe comorbidities in general in people aged under 50 years were considered.

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

- people with severe cardiovascular, renal and lung conditions would have similar risk of hospitalisation due to COVID-19 as people with CF, and were also likely to require a combination of three or more high-risk medical conditions in order to access funded community COVID-19 treatments, and

- although there is a high overall health need for people with CF, other conditions also resulted in declines in and reduced in lung function including COPD and non-CF bronchiectasis, and these conditions disproportionately affect Māori and Pacific peoples, and
- other conditions specified in the criteria (Down syndrome and sickle cell disease) have good disease-specific evidence for health need for these conditions, but evidence for health need and benefit in CF is of poor quality and strength.

2.4. The Advisory Group **declined** the addition of CF to the pre-exposure prophylaxis access criteria allowing access to tixagevimab with cilgavimab (Evusheld).

2.5. The Advisory Group considered that the use of tixagevimab with cilgavimab pre-exposure prophylaxis would be inappropriate, as benefit is only seen in people who have not adequately responded to vaccination or who are not able to be vaccinated due to a medical contraindication, which members considered would not apply to the majority of people with CF.

2.6. The Advisory Group noted that the current access criteria for tixagevimab with cilgavimab enabled access for severely immunocompromised people, including people who had received a lung transplant. The Group considered this would include the people with CF most at risk of severe illness following COVID-19 infection.

Discussion

Māori impact

2.7. The Advisory Group noted that CF is a genetic disease resulting in lung function decline, affecting mostly those of European decent genetically. The Group considered other lung diseases that result in lung function decline, such as non-CF bronchiectasis or COPD, would have similar risk of severe illness to people with CF following COVID-19 infection, and noted that Māori and Pacific peoples are over-represented in the prevalence of these conditions with significantly larger affected populations. The Group considered that the consideration of diseases that result in progressive decline in lung function should be wider than only those with CF, noting the need for equitable access.

Health Need

2.8. The Advisory Group noted that those with CF are a relatively small group with an estimated 500 people affected in New Zealand, with half aged younger than 18 years (49.7% of those with CF). The Group noted that CF is a genetic disease affecting mostly those of European decent genetically. The Group noted that CF is a progressive disease resulting in thick mucus secretions that affect lung function and increase the risk of chest infections. The Group noted that CF can also cause diabetes, liver disease and infertility.

2.9. The Advisory Group considered the main concern with regard to COVID-19 for people with CF to be the progressive decline in lung function measured as a decrease in forced expiratory volume (FEV1). The Group noted that exacerbations of CF are usually a result of bacterial or viral respiratory tract infections, resulting in a potential decline in lung function.

2.10. The Advisory Group considered the use of COVID-19 treatments to reduce the risk of exacerbation resulting from COVID-19 infection and potentially preserve lung function in addition to reducing the risk of severe COVID-19 and hospitalisation.

2.11. The Advisory Group considered reporting on an Australian CF registry data (Ahern et al. ACFDR Registry Annual Report, 2021. Monash University, August 2022, Report No 23)) of patient serial FEV1 lung function measured annually, which observed the average FEV1 and BMI improved in those with CF in the first year of the pandemic (2020), ascribed likely due to the lockdowns, physical distancing, and additional hygiene measures. The Group considered those with CF aged over 40 years or with FEV1<70% were the people with CF most at risk of severe COVID-19, excluding those who have received transplants, and estimated this to be 100 people managed under specialist care.

2.12. The Advisory Group considered those with CF are not at greater risk of being infected with SARS-CoV-2 compared to the general population, particularly due to shielding in this population. The Group considered those people with CF who become infected with COVID-19 are at a higher risk of hospitalisation than people infected with COVID-19 who do not have comorbidities, with variation within the CF population based on severity of their underlying CF disease. The Group noted other lung diseases also result in lung function decline, such as non-CF bronchiectasis or COPD. The Group considered that people with these conditions would also have an increased risk of severe COVID-19 and considered Māori and Pacific peoples to be over-represented in the prevalence of these conditions with significantly larger affected populations. The Group considered that access to COVID-19 treatments for people with conditions resulting in progressive lung function decline should be wider than only those with CF, noting the need for access to be equitable.

2.13. The Advisory Group considered the other conditions specified in the criteria (Down syndrome and sickle cell disease) to have good disease-specific evidence for health need for these conditions. The Group considered the evidence for health need in those with CF to be low to moderate quality and strength, with most studies conducted earlier during when the more virulent Delta variant was dominant. The Group considered that New Zealand data on hospitalisations of people with CF would be useful in assessing the impact of COVID-19 on those with CF.

Health Benefit

2.14. The Advisory Group considered there was no evidence that COVID-19 antivirals had additional benefit in those with CF compared to those that do not have CF. The Group considered it was biologically plausible that a reduction in viral load and hospitalisation risk from treatment with COVID-19 antivirals could have benefit in preserving lung function in those with CF. The Group noted that treatment with nirmatrelvir with ritonavir is not recommended in those under 12 years old, and the impact on access for those young people. The Group considered the potential for drug-drug interactions with common CF therapies to be likely but able to be managed by omitting or adjusting those therapies' doses. The Group considered that molnupiravir would unlikely be beneficial in those with CF due to maturing large-scale clinical trial evidence (Butler et al. Statnews [Epub ahead of print]. 2022 [cited 2022 October 12]) of a lack of reduction in

hospitalisation and mortality rates, and its use in those aged under 18 years being unapproved and not recommended.

2.15. The Advisory Group noted that in the PROVENT trial (Levin et al. N Engl J Med. 2022; 386:2188-200) it was reported that those at high risk of COVID-19 exposure including, but not limited to, healthcare workers, workers in industrial settings, military personnel, students in dormitories or people living in high-density or close proximity did benefit from pre-exposure prophylaxis with tixagevimab with cilgavimab. The Group considered that those most likely to benefit were those that have not adequately responded to vaccination or who are not able to be vaccinated due to a medical contraindication, as they are at highest risk of severe COVID-19 or persistent infection. The Group considered that the majority of people with CF would not be considered to be immunocompromised (in terms of the eligibility criteria for community COVID-19 antivirals) and would be expected to respond to vaccination. The Group considered that the use of tixagevimab with cilgavimab pre-exposure prophylaxis would be inappropriate in this instance.

Funding criteria

2.16. The Advisory Group considered the criteria for antivirals would enable possible access for people living with CF including transplant recipients or those with three co-morbidities such as lung function decline, sinus disease, diabetes, digestive issues or low BMI, which may affect people with CF. The Group considered those with eligible comorbidities would be a very small subgroup of those with CF but would likely be able to access COVID-19 treatments already. The Group noted feedback from the Te Whatu Ora – Health New Zealand COVID-19 Care in the Community team that the association with CF may validly be counted as one comorbidity.

2.17. The Advisory Group considered correspondence from Cystic Fibrosis NZ outlining that the requirement for three or more comorbidities in those under 50 years old excluded those with CF from access to COVID-19 treatments. The Group considered that the Ministry of Health list of comorbidities does not capture the varying risk associated with increasing severity within each comorbid condition. The Group noted unpublished, interim results of a study (Raymond et al. COVID-19 comorbidity risk factors for hospitalisation - interim results [Conference presentation]. October 2022. Australasian Society for Infectious Diseases Conference New Zealand) reporting that those with severe renal, cardiovascular or lung disease were at 2.5 times higher risk of hospitalisation than those with other comorbidities. The Group considered those under 50 years old with a singular (or only two) severe cardiovascular, renal or lung condition(s) to potentially be unable to access COVID-19 treatments despite having an increased risk of hospitalisation compared to people without comorbidities and that those with CF would likely fall into this group with insufficient counts of co-morbid conditions, alongside other young people with singular severe asthma, COPD, kidney or heart disease. The Group considered wider consideration of these other groups would be required before recommending amendments to the criteria.

3. Tixagevimab with cilgavimab for pre-exposure prophylaxis of COVID-19 cost effectiveness

Application

3.1. The Advisory Group reviewed the cost effectiveness information prepared by Pharmac staff of tixagevimab with cilgavimab for the pre-exposure prophylaxis of COVID-19.

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

Discussion

3.3. The Advisory Group noted that the cost effectiveness was only assessed for the pre-exposure prophylaxis of COVID-19 not treatment of COVID-19. The Group noted that the model was based on 6 monthly dosing of 300 mg each of tixagevimab and cilgavimab (ie 600 mg) as this had been increased by the supplier from the initial dose of 150 mg of each.

3.4. The Advisory Group noted the prevention of symptomatic infection was the model's assumed main outcome and that the model assumed a relative reduction of symptomatic infections resulted in corresponding relative reduction in hospitalisation, ICU admission and mortality. The Group considered the rate of infection, hospitalisation, and ICU admission to likely be independent of (and not proportional to) each other, which had been an optimistic modelling assumption by Pharmac staff. The Group considered the true rate of community infection in New Zealand to be much higher than that modelled by health agencies, due to likely under-reporting of positive community rapid antigen tests (RATs) and that this would dilute and reduce the effect of treatment on hospitalisation rates for COVID-19 cases.

3.5. The Advisory Group noted that the analysis is sensitive to changes in the infection rate and mortality rate. The Group considered that the reduction in symptomatic COVID-19 infections from prophylaxis with tixagevimab with cilgavimab would be similar to vaccination, in that the main effect would be in reduction in hospitalisation, however rates of symptomatic infection would remain relatively high. The Group considered that those most likely to benefit would be those who did not have an antibody response to four doses of an COVID-19 mRNA vaccine. The Group considered that most transplant patients (estimated to be 80%) would have an antibody response to vaccination depending on the time since their transplant, immunosuppressive therapy (in particular mycophenolate) and treatment for graft rejection. The Group considered that the cost-effectiveness would be improved if the group for funding included only those who were not able to respond to vaccination, an estimated 20% of the currently funded group. The Group considered advice from NICE on tixagevimab with cilgavimab pre-exposure prophylaxis being reserved for those who are not able to respond to COVID-19 vaccination and the assessment of use of antibody testing to identify people who would likely benefit.

3.6. The Advisory Group noted its previous recommendation to include antibody testing in the funding criteria for tixagevimab with cilgavimab, particularly that this was not included in the current criteria due to lack of clarity on the relationship between antibody titre and immune response and potential equity concerns in accessing testing services.

3.7. The Advisory Group noted that infection rate estimates made by Pharmac were based on recent trends in COVID-19 infection in New Zealand and subject to significant uncertainty as new Omicron variants of concern emerge in New Zealand. The Group noted that the evidence of effectiveness of tixagevimab with cilgavimab was based on the PROVENT trial (Levin et al. N Engl J Med. 2022;386(23):2188-200) and an additional study in vaccinated solid organ transplant patients during the Omicron BA.1 and BA.2 wave (Al Jurdi et al. Am J Transplant. [Epub ahead of print] 2022). The Group noted that the PROVENT trial was conducted from November 2020 to March 2021 and that the change in circulating SARS-CoV-2 variants would impact the relevance of these results on the efficacy of tixagevimab with cilgavimab in the current Omicron variant environment. The Group also considered that the strength of evidence from the Al Jurdi et al. study was not strong, as it was a non-randomised open label study. The Group considered that those included in the treatment group would already be committed to the reduction of infection risk and would confound the comparison between the groups.

3.8. The Advisory Group considered the likelihood of death from COVID-19 in ICU in the current Omicron variant environment to be low. The Group considered that most COVID-19 admissions into ICU were now incidental and that case fatality during Omicron waves was lower than in Delta variant dominance. The Group considered that those most likely to be hospitalised from COVID-19 are older people, those with at-risk co-morbidities and those who are immunocompromised. The Group noted that those targeted for tixagevimab with cilgavimab pre-exposure prophylaxis are those who are immunocompromised and not expected to respond to vaccination against COVID-19, and considered that most hospitalised people would not be eligible for pre-exposure prophylaxis with tixagevimab with cilgavimab. The Group noted uncertainty with the cost of hospitalisation but that this was not particularly material as the analysis was not sensitive to the estimated cost.

3.9. The Advisory Group noted that the analysis was sensitive to infection rate. The Group considered that different SARS-CoV-2 variants would have different rates of infection and would change the efficacy of tixagevimab with cilgavimab, however the Group was not able to anticipate the likely infection rate or efficacy of tixagevimab with cilgavimab in future variants. The Group considered that during October 2022 the efficacy was estimated as 80-90% against circulating variants however, there was likely no efficacy against the Omicron BA.4.6 variant which is increasing in the Northern Hemisphere. The Group considered the trends of circulating variants in New Zealand will likely follow the Northern Hemisphere.

3.10. The Advisory Group considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for tixagevimab with cilgavimab cost-effectiveness analysis if it were to be considered further for funding in New Zealand for pre-exposure prophylaxis of COVID-19. This PICO captures key clinical aspects of the proposal and may be used to reframe any future economic assessment by Pharmac staff. This PICO is based on the Group's assessment at this time. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	
Intervention	Tixagevimab with cilgavimab 600mg given 6-monthly + best supportive care (BSC) (antiviral therapy – nirmatrelvir with ritonavir (Paxlovid) or molnupiravir)
Comparator(s)	BSC + antiviral therapy (nirmatrelvir with ritonavir (Paxlovid) or molnupiravir)
Outcome(s)	Prevented symptomatic cases + GP visit and antiviral therapy Hospitalisation/ICU Mortality Health related quality of life
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.	

Molnupiravir for treatment of COVID-19 – evidence update

Application

3.1. The Advisory Group reviewed the new evidence for molnupiravir in the treatment of COVID-19.

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

Recommendation

3.3. The Advisory Group recommended that, based on the information available, nirmatrelvir with ritonavir or remdesivir are the preferred antiviral treatments for people with COVID-19, and molnupiravir should only be considered when both nirmatrelvir with ritonavir (Paxlovid) or remdesivir are not accessible or are clearly clinically inappropriate.

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

- New information from the unpublished preliminary analysis of the open label, randomised, controlled PANORAMIC trial reporting no reduction in combined hospitalisations/deaths overall in an Omicron variant environment

- Given the currently available data regarding the effectiveness of nirmatrelvir with ritonavir (Paxlovid) and remdesivir in the treatment of COVID-19, the use of molnupiravir instead of an alternative COVID-19 treatment (when such alternatives were clinically appropriate), could mean denying people access to a more effective therapy,

- It cannot be ruled out that use of molnupiravir may offer some benefit for people who cannot, for strong clinical reasons, receive nirmatrelvir with ritonavir (eg at risk of poor health outcomes both from COVID-19 and clear drug interactions that cannot be managed by dose reduction etc), compared with no treatment.

Discussion

Māori impact

3.5. The Advisory Group noted the use of molnupiravir in Māori to be higher than for nirmatrelvir with ritonavir, and considered the use of molnupiravir in Māori potentially denied them access to nirmatrelvir with ritonavir when not contraindicated or inappropriate. The Group considered this an important health equity issue.

Health Benefit

3.6. The Advisory Group considered the guidance from the Indian regulator, the Central Drugs Standard Control Organisation, based on 12 unpublished and publicly unavailable RCTs (13,000 participants), including two studies that were discontinued, using generic molnupiravir (Mahase E. BMJ 2022; 378:o2063). The Group noted that molnupiravir is not included in the Indian Council of Medical Research COVID-19 treatment guidelines (Ministry of Health and Family Welfare, India. Clinical Guidance for Management of Adult COVID-19 Patients. Updated: 14 January 22). The Group considered that the omission of this evidence left a significant gap for trials of generic molnupiravir efficacy.

3.7. The Advisory Group considered the evidence from an unpublished Israeli retrospective cohort study in a large healthcare organisation (HCO) covering 65% of the older Israeli population, comparing 1,069 non-hospitalised high risk molnupiravir recipients with 18,799 corresponding non-recipients (Arbel et al. [Epub ahead of

preprint 2022]]), sourced from 1.17 million HCO members with COVID-19 from January to March 2022. The Group noted that those included in the study were not able to take nirmatrelvir with ritonavir due to chronic kidney disease or drug-drug interactions. The Group noted that testing the interaction of molnupiravir treatment status with the other variables revealed a significant interaction with age group (at/above or below 65 years; multivariate Cox proportional-hazards regression adjusted hazard ratio (HR) 1.55 (95% CI 1.32 to 1.82) for ages ≥65 vs. <65 years), and hence outcomes were reported separately for the two age groups. The Group noted no hospitalisation benefit associated with molnupiravir use was reported in the under 65-year-old group (8/124 hospitalisations/molnupiravir users vs. 97/3613 non-users, adjusted HR 1.80 (95% CI, 0.86 to 3.8)), who instead experienced an increase in mortality that was statistically significant (adjusted HR 12.8 (95% CI, 3.4 to 48.2)). The Group noted however a benefit with statistically significant reductions in hospitalisations (18/945 vs 513/15186, adjusted HR 0.55 (95% CI 0.34 to 0.88)) and reduced mortality rates in those aged 65 years and over.

3.8. The Group noted that there was a considerable ethnic disparity in those who were treated relative to the general Israeli population, with the majority of participants being classified as general Jewish and smaller proportions being classified as Arab or Ultra-Orthodox Jewish. The Group considered that this may be contributing to the beneficial outcomes seen in this group. The Group noted that not all of the eligible group were treated with molnupiravir, and it was unclear why this was so. The Group noted that uptake of molnupiravir was higher amongst people of higher economic status and considered that those who were treated potentially had access to more resources than those not treated despite being eligible.

3.9. The Group expressed concerns regarding the statistical analysis used in the Arbel et al. 2022 study, noting that the decision of the authors to assess the population as those at/over versus under 65 years of age, rather than using a younger age bound, could be influencing the statistically significant results reported in the over 65 age group.

3.10. The Advisory Group considered the AGILE CST-2 study (Khoo et al. Lancet Infect Dis. [Epub ahead of print] 2022) comparing viral load effect of molnupiravir with placebo, which reported that those randomised into the molnupiravir arm were quicker to return a negative nasopharyngeal swab, at a mean of day 8 compared to day 11 in the placebo arm. The study also reported a reduction in viral load in the molnupiravir group at day 5 but without any measurable clinical effect. The Group noted that at day 15 the proportion of COVID-19 negative participants was similar, and investigators considered molnupiravir had moderate anti-viral activity with inconclusive evidence of clinical benefit. The Group noted that molnupiravir did not meet the prespecified threshold for superiority to progress to an RCT for this study (reporting a 75.4% probability of molnupiravir being superior to placebo, compared to a prospective 80% threshold being evaluated).

3.11. The Advisory Group noted the unpublished preliminary analysis of the open label randomised PANORAMIC platform adaptive multi-arm trial testing multiple COVID-19 treatments simultaneously (Butler et al. Statnews [Epub ahead of print]. 2022]), with 25,000 participants with COVID-19 recruited from December 2021 to April 2022 with the primary outcome of all-cause hospitalisation or mortality. The Group noted that study included those over 50 years old or those over 18 years old with comorbidities. The participants had a mean age of 56.6 years, and 9% of participants had a weakened immune system (undefined). The Group noted that there was no statistically significant difference in hospitalisation rate or death between treatment arms (adjusted odds ratio (aOR) 1.06 (95% CI 0.80 to 1.40)). The Group noted the time to recovery was significantly less with molnupiravir, but also noted the open-label design of the study and tempering potential impact of a placebo effect.

3.11.1. Related to PANORAMIC's reported reduced recovery time with molnupiravir, the Group noted contradictory results from other trials of antivirals. The Group noted the EPIC-SR trial (ClinicalTrials.gov Identifier: NCT05011513), an open-label study reporting on the time to recovery for standard-risk people treated with nirmatrelvir with ritonavir (Paxlovid), which reported no benefit in symptom resolution in the group treated with nirmatrelvir with ritonavir (Paxlovid) when compared to usual care and which was terminated due to the low hospitalisation and mortality rate in this group (Pfizer press release. 14 June 2022). The Group considered that supplementary final results from the MOVe-OUT study (Bernal et al. N Engl J Med. 2022;386(6): Supplementary Appendix) reported largely no differences in symptom resolution in standard risk patients when treated with molnupiravir. The Group therefore considered the validity of the PANORAMIC result, in light of the contrary results of these studies. Members considered that nirmatrelvir with ritonavir would be expected to have similar or higher virological impact than molnupiravir, and considered it likely there was a placebo effect distorting the reported lessened time to recovery with molnupiravir in the PANORAMIC study.

3.11.2. The Advisory Group also noted PANORAMIC's molnupiravir arm had reduced contact with primary care in the community but no reduction in contact with emergency departments.

3.11.3. The Group noted the subgroup analysis for PANORAMIC, in particular, non-significant hospitalisation/death reductions in those aged over 80 years (aOR 0.47 (95% BCI 0.16,1.39)) and those with diabetes (aOR 0.59 (95% BCI 0.29,1.22)) but contrasting non-significant increases in those with a compromised immune system (aOR 1.88 (95% BCI 0.96,3.69)) and those who received treatment after having symptoms for longer than three days.

3.11.4. The Group noted that at this time there had been no changes to international guidelines resulting from the release of the preprint of the PANORAMIC trial, noting that international guidelines (which include molnupiravir) at the time of the meeting largely recommended molnupiravir only when nirmatrelvir with ritonavir (Paxlovid) or remdesivir are not available, are not feasible to use, or are not clinically appropriate.

3.11.5. The Group considered the strength and quality of the PANORAMIC evidence to be high, due to the large number of participants and randomised, controlled design of the trial.

3.11.6. The Advisory Group considered that the safety of molnupiravir was not assessed in PANORAMIC, and therefore the risk of taking molnupiravir for those who are not considered at high-risk of hospitalisation or death is unknown.

3.12. The Advisory Group also considered that the clinical recommendations for use of effective contraception with molnupiravir treatment (during treatment and 4 additional days for women and during treatment and an additional three months for men with a partner of childbearing potential) could be difficult to manage for some patients.

3.13. The Advisory Group considered the low rate of pneumonitis and hospitalisation with the current Omicron variant was a barrier to being able to observe any a reduction in hospitalisation rates, as (baseline) hospitalisation is estimated to be 1% without intervention. The Group considered that all-cause hospitalisation in an Omicron environment compared to a Delta variant environment would likely occur in older people who are more frail and less physically resilient. The Group considered that people experiencing hospitalisation specifically due to COVID-19 (as opposed to co-incidental or all cause hospitalisation) would be a very small group and it would be difficult to show unequivocal efficacy statistically.

3.14. The Advisory Group considered correspondence from the supplier and the information provided regarding retrospective studies from Hong Kong (Wong et al. preprint 2022, 26 May, Wong et al. Lancet Infect Dis. [Epub ahead of print 2022,24 August]) previously considered at the August 2022 meeting and (Arbel et al. [Epub ahead of preprint 2022]). The Group considered the randomised, controlled design of the PANORAMIC trial to be superior quality and strength compared to the retrospective studies and considered that greater emphasis should be placed on the results of the PANORAMIC trial.

3.15. The Advisory Group was informed of national antiviral dispensing data, where the mean age of dispensing of molnupiravir in New Zealand was 71 years, contrasting with the mean age of all those included in the PANORAMIC study of 56.6 years. The Group was informed that those who had been dispensed molnupiravir to date had been 91.2% fully boosted (3 or more doses), a further 5.3% fully vaccinated (full primary course) and 3.5% unvaccinated. The Group was informed the use of molnupiravir relative to nirmatrelvir with ritonavir was proportionately higher in Māori and Pacific cases than non-Māori non-Pacific cases, and considered the possible relative overuse of molnupiravir in Māori and Pacific peoples potentially denied them access to effective treatment with nirmatrelvir with ritonavir (Paxlovid). The Group considered this an important equity issue for Māori and Pacific peoples, whilst acknowledging the higher burden of comorbidities that disproportionately affect Māori and Pacific peoples (where that additional comorbidity in Māori and Pacific peoples renders nirmatrelvir with ritonavir potentially relatively more unsuitable for Māori and Pacific peoples because of unmanageable drug/drug interactions, correlated with comorbidities, thus more frequently confining their treatment options to molnupiravir).

3.16. The Advisory Group considered the main purpose of oral antiviral treatments was to reduce hospitalisations and deaths and considered that the presented evidence for molnupiravir was unsupportive of this overall. The Group noted a concern that, primary healthcare providers may be less likely to give nirmatrelvir with ritonavir due to potential harms, complexity and the substantial time it takes to assess for drug-drug interactions when prescribing nirmatrelvir with ritonavir. The Group considered the risk of prescribing a potentially ineffective therapy in place of a potentially effective therapy (where that effective therapy was suitable and safe and any clinically significant drug-drug interactions were managed) to be harmful to those eligible and clinically suitable for funded antivirals. The Group considered the valuable role of pharmacists in assessing potential drug interactions and utilising their influence to reduce the use of molnupiravir amongst people who could receive nirmatrelvir with ritonavir.

3.17. The Advisory Group noted that as age increases so do comorbidities (with associated medicines use) and molnupiravir use, based on New Zealand dispensing data. Some Members considered there may be a role for molnupiravir in the community for people who have no other treatment option and thus their alternative is no COVID-19 antiviral treatment (ie. where nirmatrelvir with ritonavir is categorically unsuitable because of drug interactions that are potentially clinically important; remdesivir logistically challenging). The Group noted that the remaining molnupiravir stock secured by Pharmac may continue to be available for eligible people in New Zealand who are unable to receive nirmatrelvir with ritonavir due to clinical reasons at this current time.

3.18. The Advisory Group considered there is a need to strengthen prescriber education regarding the Group's preference for the use of nirmatrelvir with ritonavir (Paxlovid) and remdesivir over molnupiravir for the treatment of COVID-19 in light of the new, currently unpublished, data. The Group noted that there is an existing note in the COVID-19 antiviral access criteria that alludes indirectly to using nirmatrelvir with ritonavir ahead of molnupiravir, stating "Consider molnupiravir or remdesivir if

nirmatrelvir with ritonavir is unsuitable or unavailable". Members considered the wording could be made explicit, to ensure nirmatrelvir with ritonavir was truly contraindicated and remdesivir was not locally accessible, before considering molnupiravir in a small subset of patients. Members considered potentially excluding access to molnupiravir for immunocompromised and younger people where there may be net harm.

3.19. The Advisory Group discussed the possibility of limiting funded access to molnupiravir to a smaller subset of people currently eligible for funded antivirals; however, the Group considered there was a risk that this could be interpreted as promoting molnupiravir to this group over other, more effective treatment options and therefore did not recommend this approach, preferring prescriber education or guideline promotion.

3.20. The Advisory Group considered that any education should not be directed at the public, to avoid discouraging people from accessing treatment. The Group considered the direct-to-consumer marketing of molnupiravir to be a potential concern, as it could encourage expectations by the public for molnupiravir over nirmatrelvir with ritonavir.