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.

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

Attendance

Present
Chair – Dr Jane Thomas
Professor Brian Anderson
Dan Bernal (Te Whatu Ora observer)
Eamon Dufy
Gareth Frew (Te Whatu Ora observer)
Dr Gillian Hood
Dr Justin Travers
Associate Professor 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

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.