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 31 October 2022

Attendance

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

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.