Excerpt from Record of the COVID Treatments Advisory Group
Meeting held on 30 May 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.

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Attendance

Present
Chair – Dr Jane Thomas
Dr Ajay Makal
Professor Brian Anderson
Dr Gillian Hood
Dr Graham Mills
Dr Nigel Raymond
Professor Stephen Munn
Dr Tim Cutfield

Apologies
Eamon Duffy
Dr Justin Travers
Dr Kerry Benson-Cooper
Associate Professor Marius Rademaker
Dr Robyn Manuel

1. Sabizabulin for severe COVID-19 at risk of acute respiratory distress syndrome (ARDS)

Application

1.1. The Advisory Group reviewed the information provided by the supplier and Pharmac relating to sabizabulin for the treatment of severe COVID-19 at risk of acute respiratory distress syndrome (ARDS).

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

Recommendation

1.3. The Advisory Group **deferred** its recommendation on sabizabulin for the treatment of severe COVID-19 at risk of ARDS until further information was available.

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

- It is likely that the size of the group of people who would require treatment with sabizabulin would be very small.
- The low intensive care unit (ICU) admission and mortality rate currently observed in New Zealand, as a result of the less severe Omicron variant(s) currently circulating.
- The benefit from sabizabulin reported in the published interim analysis
- The US Food and Drug Administration (FDA) review of sabizabulin, and recommendation for a larger study indicating that there may be further evidence available in the future.

Discussion

Māori impact

1.5. The Advisory Group discussed the impact of funding sabizabulin for the treatment of severe COVID-19 at risk of ARDS on Māori health areas of focus and Māori health outcomes. The Group considered that overall Māori are at higher risk of severe COVID-19 than non-Māori. The Group considered that there would be very few people in need of this treatment, due to lower risk of severe COVID-19, and mortality in the Omicron variant era.

Background

1.6. The Advisory Group noted the previous considerations of tocilizumab and baricitinib in April 2021 and October 2021 respectively, which are used in a similar group as has been proposed for sabizabulin. The Group noted that these recommendations resulted in the restriction of funding of the treatments in hospitals, only for people with moderate to severe COVID-19, with an oxygen saturation of <92% on room air or requiring supplemental oxygen, and receiving adjunct systemic corticosteroids or are contraindicated.

Health need

1.7. The Advisory Group noted that the Ministry of Health (Manatū Hauora) (Clinical Management of COVID-19 in Hospitalised Adults) guidelines defined those with moderate COVID-19 as 'any clinically stable person with evidence of pneumonitis and hypoxia that is sustained but able to maintain ≥ 92% (≥90% for patients with chronic lung disease) with up to 4L/min oxygen via standard prongs', and severe as a person with any of the following: 'requires CPAP or high flow oxygen, acute respiratory distress (respiration rate >30) or rapidly deteriorating'.

1.8. The Advisory Group considered those presenting at hospital have symptoms relating to the viral infection such as pneumonitis or bronchiolitis and the inflammatory immune response to the virus.

1.9. The Advisory Group considered that the government COVID-19 response was well established, with most of the New Zealand population being vaccinated, and people at risk having access to funded COVID-19 antivirals. The Group considered that there are fewer people being admitted to ICU for COVID-19, and lower overall mortality from COVID-19, than in earlier phases of the pandemic. The Group considered that the need for this treatment was unclear.

Health benefit

1.10. The Advisory Group noted that sabizabulin disrupts microtubules, halting viral transport, and suppressing cytokine production and release. The Group noted that this agent is also is being trialled for cancer treatment.

1.11. The Advisory Group noted the supplier proposed treatment paradigm where anyone hospitalised and requiring supplemental or high flow oxygen, could be eligible to receive this treatment. The Group noted that this treatment would be used in combination with corticosteroids (dexamethasone) and in place of other alternatives (baricitinib or tocilizumab, with or without remdesivir). The Group considered that sabizabulin could be used in those who have respiratory compromise, but not yet on a ventilator, as they are at high risk of progressing to ARDS due to their comorbid medical conditions, the speed of their disease progression, or where baricitinib and tocilizumab are not available.

1.12. The Advisory Group noted the published interim analysis for oral sabizabulin for high-risk, hospitalised adults with COVID-19 analysed 150 of 204 participants treated up to day 21, or until discharge, and followed up to day 60 (Barnette et al. NEJM Evid 2022;1(9)).

1.12.1. The Group considered that the age of participants was 61.3 years for sabizabulin and 62.7 years for placebo.

1.12.2. The Group noted that the primary endpoint was death up to day 60, while key secondary endpoints were the proportion of participants alive without respiratory failure at days 15, 22, 29 and 60, days in ICU, days on mechanical ventilation, days in hospital, proportion of participants who died at day 15 22 and 29 and change in viral load from baseline to day 9 and baseline to the day last on study.

1.12.3. The Group noted that the primary endpoint of mortality at day 60 was met, and that there was a decrease in the mortality reported in those treated with sabizabulin compared to placebo (odds ratio (OR) 3.21, 95%CI 1.45-7.12, *P*=0.004).

1.12.4. The Group considered death at day 60 to be the most robust endpoint.

1.12.5. The Group considered that the mortality rates in New Zealand with Omicron are much lower than the rates reported in the analysis.

1.12.6. The Group noted the study was conducted in 2021 and early 2022. The Group noted that the investigators separated participants based on date of randomisation as to the predominant circulating variant at that time. The Group considered that the relative effect on mortality was similar regardless of variant, considering that mortality has decreased with evolving Omicron variants.

1.12.7. The Group considered that there was no subgroup that clearly benefitted more than others, and that some subgroups had small

numbers of participants included, making interpretation of these results unclear.

1.12.8. The Group considered that although this is only preliminary data, the primary and secondary outcomes chosen were suitable, and that overall the reported benefit from the trial seems supportive.

1.12.9. The Group considered the currently published preliminary outcome data was not sufficient to be able to make a recommendation. The Group considered that further studies are required to generate larger, more mature data.

1.13. The Advisory Group considered that people who are hospitalised and receiving oxygen via an oxygen mask or nasal prongs (WHO Ordinal Severity Score 4), or via non-invasive mechanical ventilation or via a high-flow nasal cannula (WHO 5) would likely receive the most benefit from sabizabulin treatment.

1.14. The Advisory Group considered that the benefit of sabizabulin was uncertain in people who are hospitalised and require intubation and mechanical ventilation (WHO 6) due to low numbers of those requiring mechanical ventilation included in the trial.

1.15. The Advisory Group considered that those who are at higher risk of severe COVID-19 include people with high-risk comorbidities, older age, or Māori and Pacific ethnicity.

1.16. The Advisory Group noted that there were no other trials of sabizabulin in COVID-19, and there were no trials directly comparing to other regimens. The Group considered that the standard of care differed between the centres enrolled in the study and therefore unable to easily compare regimens. The Group considered that New Zealand has established protocols, and ICU standard of care is uniform across New Zealand, and not comparable to the countries of centres included in the study (US and Brazil).

1.17. The Advisory Group considered that New Zealand is a highly vaccinated population, with antivirals available to reduce viral load and decrease risk of hospitalisation in people who are at risk.

1.18. The Advisory Group noted that corticosteroids, Janus-associated tyrosine kinase inhibitor (JAK inhibitor), and biologic treatments are also available for treatment of people who are hospitalised and require immune modulation therapy.

1.19. The Advisory Group considered that the use of sabizabulin would be in a small group of people, as the risk of ARDS in a highly vaccinated population is low. Further, the Group considered people at high risk have access to funded COVID-19 antivirals, and there is a low prevalence of pneumonitis and mortality in the Omicron variant era.

1.20. The Advisory Group noted that at the time of the meeting there had been regulatory submissions for sabizabulin to the FDA, European Medicines Authority (EMA) and the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium.

1.21. The Advisory Group noted that sabizabulin had been reviewed by the FDA, which resulted in a recommendation of a larger, more methodologically robust study to address the following concerns:

- the small sample size limiting ability to identify clinically significant safety signals
- high placebo group mortality rate

- potential for unblinding events with enteral tube administration
- baseline imbalances in standard of care therapies
- differences in hospitalisation duration prior to trial enrolment
- uncertainty as to the effects of goals of care decisions on all-cause mortality
- other studies with other microtubule disruptors (eg colchicine) in treatment of COVID-19 were negative
- uncertainty in identification of a clinically relevant patient population
- sensitivity analysis not sufficient to adjust for baseline imbalances.

Suitability

1.22. The Advisory Group noted that the oral capsule formulation of sabizabulin was not appropriate for those intubated or unable to take solid oral dosage forms.

1.23. The Advisory Group noted that the supplier suggested that the contents of the capsule (not the capsule shell) be mixed with 20 mL of water and administered via a nasogastric tube (French gauge 8 or larger) followed by 40 mL of water to rinse.

1.24. The Advisory Group considered that people in ICU have reduced gastric motility, and that there could be decreased absorption of sabizabulin via the oral route when delivered via a nasogastric tube.

Cost and savings

1.25. The Advisory Group noted its previous advice from October 2021, that 4% of all symptomatic COVID-19 cases would access baricitinib or tocilizumab.

1.26. The Advisory Group noted that during the 7 days ending 22 January 2023, the number of new cases reported (assumed symptomatic) was 13,874, with 19177 and 23125 cases notified in the preceding week and fortnight respectively. The Group noted there were 242 cases in hospital and 7 in ICU that night (22 January). The Group considered that the apparent proportion of hospitalised cases (242 ÷ 13880 to 23125 = 1.0% to 1.7%) at that time in January seemed less than initially estimated, and that not all of these cases would be eligible for sabizabulin treatment ie requiring supplementary oxygen.

Summary for assessment

1.27. The Advisory Group noted that elements of the PICO (population, intervention, comparator, outcomes) for this application are unclear/uncertain at this time. The PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff.

2. Molnupiravir consultation feedback

Application

2.1. The Advisory Group reviewed the consultation feedback regarding the role of molnupiravir in New Zealand's funded treatments portfolio for COVID-19.

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

Recommendation

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

2.4. The Advisory Committee considered the following in making this recommendation:

- The potential effect of recommending discontinuing funding would be re-direction of prescribing to more effective treatments.
- The majority of the evidence was prospective and retrospective cohort studies, with important issues relating to potential biases in these studies inherent with less robust methods, requiring caution in interpreting them, particularly in the context of New Zealand's pandemic response and health outcomes.
- Clinical trials were not powered to show mortality risk in high-risk groups who would be most likely to benefit, such as people with multiple comorbidities or older people (more likely at risk of medicine interactions or renal impairment contraindicating other community COVID-19 antivirals).

Discussion

Māori impact

2.5. The Advisory Group discussed the impact of delisting molnupiravir for the treatment of COVID-19 on Māori health outcomes. The Group noted that previously age-specific rates of dispensing of molnupiravir had been higher in Māori with COVID-19 compared to non-Māori cases. The Group noted that although the prescription rate of molnupiravir had decreased in Māori, there had not been a similar increase in the prescribing of nirmatrelvir with ritonavir. The Group considered that there is inequity in the prescribing of these medicines, but queried if molnupiravir is the best option to fill this inequity. The Group considered that it would not be fair to use a less effective treatment to reduce inequities between Māori and non-Māori.

Background

2.6. The Advisory Group noted its previous considerations of evidence for the benefit of molnupiravir in August, October 2022 and February 2023 including the MoVe-OUT (Jayk Bernal et al. N Engl J Med 2022;386:509-20) and PANORAMIC (Butler et al. Lancet. 2023;401:281-93) randomised controlled trials.

2.7. The Advisory Group noted the Te Whatu Ora clinical guidelines recommending that molnupiravir not be used for the treatment of COVID-19.

Health Need

2.8. The Advisory Group considered that in the general population the risk of mortality from COVID-19 is now very low, however those who are at most risk of dying from COVID-19 are most likely to be immunocompromised. The

Group considered that for those who are immunocompromised, molnupiravir would not be expected to provide benefit.

2.9. The Advisory Group considered that the majority of people eligible to access funded antivirals should be treated with options other than molnupiravir. The Group considered the group of people that are unable to have other COVID-19 antiviral options (due to unmanageable drug interactions, renal impairment or inability to access intravenous treatment) would be small. The group considered this group would have an unmet health need, if they were at risk of more severe COVID-19 disease, regardless of the availability of molnupiravir. Members considered that the anticoagulants were the most common interaction potentially contraindicating (or at least complicating) the use of other antivirals. The Group considered these were commonly prescribed in older people.

2.10. The Advisory Group discussed the impact of delisting molnupiravir for the treatment of COVID-19 on Māori health outcomes. The Group noted that previously, age-specific rates of dispensing of molnupiravir had been higher in cases who were Māori compared with non-Māori cases. The Group noted that although the prescription of molnupiravir had decreased in Māori there had not been a similar increase in prescribing of nirmatrelvir with ritonavir to balance this. The Group considered that there is inequity in the prescribing of these medicines but queried if molnupiravir is the best option to fill this inequity. The Group considered that it would not be fair to use a less effective treatment to reduce inequities between Māori and non-Māori.

2.11. The Advisory Group considered that recommending the discontinuing of funding of molnupiravir may result in a re-direction of prescribing to more effective treatments.

Health benefit

2.12. The Advisory Group considered additional evidence for molnupiravir, previously not considered, provided by the supplier:

- Najjar-Debbiny et al. Clin Infect Dis. 2023;76:453-60
- Bajema et al. [Preprint]. 2022
- Evans et al. J Infect. 2023;86:352-60
- Gentry et al. J Infect. 2023;86:248-55

2.13. The Advisory Group also noted that there were retrospective cohort data from the Victorian State Department of Health, Australia on hospitalisation and mortality when treated with oral antivirals. The Group noted that at the time of the meeting this information was not publicly available, but has since been released as a preprint publication (Van Heer et al. [Preprint]. 2023).

2.14. The Advisory Group noted that presented evidence did not include evidence relating to molnupiravir that was reviewed at earlier meetings.

2.15. The Advisory Group noted the following additional prospective and retrospective cohort studies relating to the efficacy of molnupiravir, in the treatment of mild to moderate COVID-19:

- Xie et al. BMJ. 2023;381:e074572
- Wong et al. Lancet Infect Dis. 2022;22:1681-93
- Yip et al. Clin Infect Dis. 2023;76:e26-e33
- Wong et al. Lancet. 2022;400:1213-22
- Zheng et al. BMJ 2022;379:e071932

- Mutoh et al. Viruses 2023;15:811
- Lui et al. JAMA Netw Open. 2023;6:e2314393
- Evans et al. J Infect. 2023;86:352-60
- Ma et al. JAMA Netw Open. 2023;6:e2310887
- Bajema et al. Ann Intern Med. 2023;176:807-16
- Gentry et al. J Infect. 2023;86:248-55
- Najjar-Debbiny et al. Clin Infect Dis. 2023;76:453-60

2.15.1. The Advisory Group noted that reported outcomes and magnitude of benefit varied in each study. but overall the presented cohort studies reported molnupiravir treatment to be beneficial.

2.16. The Advisory Group noted that the majority of the evidence were cohort studies. The Group considered that there were important issues relating to potential biases in these studies, which required caution in interpreting the results. The Group noted or considered for COVID-19 cohort studies:

2.16.1. potential issues included recruitment biases, the lack of fully matching potential confounders in controls, methods used, outcome definition and variability, COVID-19 variant environment, and publication bias

2.16.2. recruitment biases included bias in diagnosis and antiviral treatment

2.16.3. there were potential biases when considering who is able to access testing (RAT or PCR), sensitivity of testing and false negative RAT results, and likelihood to report test results via the Unite against COVID-19 website (the national website for reporting RAT results).

2.16.4. ability to access a health practitioner able to prescribe the appropriate antiviral, was a potential source of bias

2.16.5. the choice of antiviral given was a potential source of bias. Of the currently funded oral antiviral options, molnupiravir has less interactions with common medications, so requires less tailoring of current medication than nirmatrelvir with ritonavir

2.16.6. potential confounders included partially measured risks, including comorbidities based on clinical notes compared to what is known to prescribers. Other unmeasured risks include:

- behavioural influences on seeking healthcare,
- antiviral criteria and prescriber targeting of those at highest risk of hospitalisation or death
- other determinants of hospitalisation (social situation, geographic or deprivation)
- goals of care in very elderly or people with advanced disease compared with those with longer life expectancy

2.16.7. the measurement or definition of outcomes could bias reported results in the reviewed cohort studies. Hospitalisation as an outcome was variable and could be defined as any of the following: COVID-associated hospitalisation where incidental COVID-19 cases are excluded, inclusion of emergency department (ED) interactions as hospitalisations, or exclusion of those diagnosed in ED or as inpatients

2.16.8. people who have already started antivirals before hospitalisation, and the appropriate amount of time before being included in the treatment group, was potentially variable between studies

2.16.9. changing clinical presentation with changing SARS-CoV-2 variants would affect comparability over time. For example, the incidence of pneumonitis in COVID-19 (which was the leading cause of death with earlier SARS-CoV-2 variants) has reduced compared to other complications (with lower mortality and ICU admission rates), meaning reductions in overall case severity over time. This means that the hospitalisation rate in both treated and untreated groups is reduced.

2.16.10. total mortality was generally a consistent and reliable outcome but there are delays in registering and recording deaths. Attributable mortality (the assignment of COVID-19 associated mortality) is more difficult to measure objectively than all-cause mortality. It becomes harder to assign COVID-19 attributable death the longer the time from the initial infection.

2.17. The Advisory Group noted that in general, cohort studies were subject to potential biases, including lack of randomisation and blinding. The Group noted that within cohort studies, post-hoc retrospective analysis may further bias towards positive outcomes, with unblinded reporting on some outcomes and not others. The Group noted that some COVID-19 cohort studies reviewed were post-hoc analyses, making the results harder to interpret.

2.18. The Group considered that the risk of hospitalisation or death from COVID-19 has changed since the initial waves of the pandemic, relating to the emergent dominance of new SARS-CoV-2 variants over time. The Group considered that the differences in the eligibility criteria and prescribing behaviours varied between countries where observational studies and randomised trials were conducted. The Group considered that this affected the direct applicability to the New Zealand population. The Group noted that, unlike randomised controlled trials, cohort studies did not have a registry database of pending studies with declared methods, and considered that this could create a publication bias towards positive results only.

2.19. The Advisory Group considered that *in vitro* molnupiravir retained its antiviral activity against Omicron sub-lineages.

2.20. The Group noted that of the clinical trial evidence reviewed previously:

2.20.1. The MoVe-OUT trial (Jayk Bernal et al. 2022) had reported moderate reductions in hospitalisation and mortality, a faster decline in viral load and reduced time to viral clearance, but had too few deaths to analyse for statistically significant effects on mortality;

2.20.2. the PANORAMIC trial (Butler et al. 2023):

- was conducted during the Omicron variant era:
- there was no benefit for hospitalisation, although there was a more rapid time to symptomatic recovery and fall in viral loads
- the subgroup of clinically extremely vulnerable adults and people aged 70 years and over was an estimated 15% of the total study population and there were too few deaths to compare mortality
- the trial was insufficiently powered to detect effects on mortality.

2.21. The Group also noted the clinical trials conducted in India had not been published, and therefore there were substantial missing data (Lawrence et al. J Antimicrob Chemother. 2023;78:613-9).

2.22. The Advisory Group considered that the retrospective observational cohort regression/ matched analyses overall reported reduced hospitalisations with molnupiravir treatment.

2.23. The Group considered that the reviewed cohort studies and PANORAMIC trial results were contradictory. The Group considered that evidence needed to be interpreted with caution, and that cohort study evidence was of lower quality. The Group considered that these studies and analyses were likely subject to moderate to large effects of bias and confounding, resulting in the under and over-stating of the true effect of molnupiravir.

2.24. The Advisory Group understood that the Victorian State Government in Australia analyses (awaiting public release at the time of the meeting) indicated that there were reductions in mortality when COVID-19 antivirals were used to treat mild to moderate COVID-19, including molnupiravir. The Group did not have further information including patient characteristics and baseline differences between cohorts, affecting results' relevance and internal validity.

2.25. The Advisory Group considered that overall, the evidence available to date suggested that molnupiravir is a relatively less potent agent, with an effect on viral clearance and symptom resolution that is generally well tolerated. The Group noted that the main contraindication in adults was being of child-bearing potential compared to other COVID-19 antivirals that have drug interactions that require management.

2.26. The Group considered that molnupiravir is unlikely to reduce hospitalisation and mortality in most people, as reported in the PANORAMIC trial (Butler et al. 2023).

2.27. The Group considered that the clinical trials were not powered to show effects on mortality in high-risk groups, such as people with multiple comorbidities or older people. The Group considered these groups, who are at a higher risk of medicine interactions or renal impairment contraindicating use of other community COVID-19 antivirals, would be the most likely to benefit.

2.28. Members considered that these trial populations were not indicative of New Zealand practice and the group intended to be prescribed molnupiravir (i.e., those unable to be treated with nirmatrelvir with ritonavir due to unmanageable medicine interactions or renal impairment).

2.29. The Advisory Group was informed of a preliminary analysis from Manatū Hauora – (Ministry of Health) on the association between COVID-19 antiviral use with COVID-19 hospitalisation and mortality in New Zealand (at the time of the meeting analysis was not publicly available).

2.29.1. The Group noted that this analysis was a time-series analysis in those aged 65 years and over, with age-stratified risks, and regression estimates.

2.29.2. The Group noted the analysis reported that there was no evidence of a reduction in the risk for hospital admission based on antiviral uptake (no antiviral treatment risk: 7.1, 95% CI, 6.7-7.5; nirmatrelvir with ritonavir risk: 8.1, 95% CI, 7.4-8.9; molnupiravir risk: 13.2, 95% CI, 11.9-14.6) but did report a beneficial effect of antivirals on the risk of mortality due to COVID-19 (no antiviral treatment risk 5.9, 95% CI, 5.6-6.3; nirmatrelvir with ritonavir risk 2.3, 95% CI, 1.9-2.8; molnupiravir risk 5.8, 95% CI, 5.0-6.8).

2.29.3. The Group considered that the reported increase in risk of hospitalisation with molnupiravir treatment could reflect this treatment being targeted to people with greater comorbidity, frailty and medication burden. Members recommended caution be used interpreting the hospitalisation findings, due to the potential biases with hospitalisation as an indicator.