Record of the COVID Treatments Advisory Group Meeting held on 29 August 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 Marius Rademaker
Professor Brian Anderson
Eamon Dufy
Dr Gillian Hood
Dr Justin Travers
Dr Kerry Benson-Cooper
Dr Nigel Raymond
Professor Stephen Munn
Dr Tim Cutfield

Apologies
Dr Graham Mills
Dr Jessica Keepa
Dr Jane Thomas
Dr Robyn Manuel

COVID-19 Treatments Update

Application

1.1. The Advisory Group reviewed the update of information for funded 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

Māori impact

1.3. The Advisory Group noted that Māori have an equivalent or higher number of dispensings of nirmatrelvir with ritonavir (Paxlovid) and of molnupiravir (Lagevrio), per number of notified cases of COVID-19, compared to non-Māori. However, when counted against the estimated number of Māori eligible for funded antivirals, the rates are comparatively lower. The Group considered that this likely still indicates inequitable access for Māori. The Group considered there were two issues potentially contributing to these inequities.

1.3.1. Firstly, people with COVID-19 that are undiagnosed are not included in the eligible population, and is likely that a greater proportion of Māori are underdiagnosed.

1.3.2. Secondly, more Māori face increased barriers accessing health care than other populations.

1.4. The Group considered it unclear whether Māori were more likely to go to a pharmacist instead of their GP, for oral antiviral treatments as the evidence for this was lacking. The Group considered it likely Māori accessed Hauora Māori providers at higher rates than other primary care providers. The Group discussed whether different mechanisms would be required to enable access to antiviral treatments for Māori. The Group noted that during the COVID-19 vaccine roll out, Hauora Māori providers facilitated the encouragement and administration of vaccines.

1.5. The Group considered how a similar network could be used to enable eligible Māori to access nirmatrelvir with ritonavir at similar rates to non-Māori, at least. The Group noted that Te Aka Whai Ora – Māori Health Authority, was working actively in this space and that the Care in the Community team at Te Whatu Ora (with Te Puni Kokiri and the Department of Prime Minister and Cabinet) also has a campaign to target those likely to be eligible, both online and in print.

Background

1.6. The Advisory Group noted reporting from the Ministry of Health (19 August 2022):

1.6.1. The Group noted that case rates of COVID-19 and wastewater RNA levels have continued to decrease nationally.

1.6.2. The Group noted that the hospital admission rate had continued to decrease since mid-July to a seven-day rolling average of 0.015 per 1000 at 7 August 2022.

1.6.3. The Group noted that from March 2022 to 14 August 2022 the age-standardised cumulative non-incidental COVID-19 hospitalisation rate for Māori was 2.5 times higher than that for both Asian and European/Other ethnicities, and the Māori cumulative age-standardised cumulative mortality rate was 2.2 times higher than European or Other, with even higher adjusted rates for Pacific peoples.

1.6.4. BA.5 continues to be the dominant subvariant accounting for approximately 91% of cases. New variants BA.2.75 and BA.4.6 have been detected in the community.

1.6.5. It is probable that infections and hospitalisations and mortality will decline and plateau, however, as viral immunity, both wild-type and vaccine-stimulated, decreases over time and if new variants become prevalent, it is expected that case rates could continue to fluctuate.

1.7. The Advisory Group noted that the funding of COVID-19 treatments remains separate to that of other medicines funded by Pharmac and assessment of these medicines has been completed outside of Pharmac's usual process for funding medicines.

Oral Antivirals

1.8. The Advisory Group noted that there was a substantial revision to the antiviral access criteria as of 18 July 2022. The Group noted that there was an increase in the rate of dispensing of oral antivirals after this date and this higher rate had been maintained since then, although case numbers had declined in recent months.

1.9. The Group noted that molnupiravir and nirmatrelvir with ritonavir had been reclassified as 'Pharmacist Only' medicines which allowed pharmacists to initiate these treatments without a prescription. The Group noted that there was an online course for pharmacists to complete prior to being able to provide either molnupiravir or nirmatrelvir with ritonavir to patients without a prescription. The Group noted that the reclassification was a temporary change for six months and would be re-reviewed by Medsafe. The Group noted that this decision was in part to ensure these treatments remained accessible over the weekends, and to provide options for population groups who might not be able to easily access a GP, noting that time from symptom onset to receiving these medicines is short (within five days) and has a direct effect on the clinical outcomes.

1.10. The Group considered that Māori and Pacific peoples in general face more barriers accessing their GP and considered that pharmacists may be more accessible, which may improve uptake amongst these groups. The Group noted the evidence for improvement of uptake with pharmacy prescribing was lacking. The Group noted that pharmacist prescribing was implemented early in Quebec, Canada which now managed the majority of its dispensing of nirmatrelvir with ritonavir via this mechanism.

1.11. The Advisory Group noted there was ample stock available for remdesivir (Veklury) for use, via Te Whatu Ora Hospitals.

Casirivimab with imdevimab (Ronapreve), and sotrovimab (Xevudy)

1.12. The Group noted that stock for casirivimab with imdevimab was available but due to its predicted reduced efficacy against currently circulating variants was not being used. The Group noted that stock is due to expire in April 2023.

1.13. The Advisory Group noted that sotrovimab was not Medsafe approved. The Group noted that the FDA had removed the emergency approval for sotrovimab in some US States, where the proportion of Omicron BA.2 is over 50%, due to the predicted appreciably reduced efficacy against the BA.2 subvariant. The Group decided that, until the Medsafe approval status of sotrovimab was resolved, the Group would make no further recommendations regarding access criteria for sotrovimab.

Tixagevimab with cilgavimab (Evusheld)

1.14. The Advisory Group noted that the access criteria for tixagevimab with cilgavimab for pre-exposure prophylaxis had been finalised by Pharmac and was due for release on

25 August 2022. The Group noted the change to the criteria since its recommendation from the June 2022 meeting where the recommended international dosing of tixagevimab with cilgavimab was doubled to 300 mg of both tixagevimab with cilgavimab. The Group noted that this was not a Medsafe approved dose.

1.15. The Advisory Group noted the planned roll out of tixagevimab with cilgavimab for community administration, in addition to hospital administration, for a small group that are not able to access it within secondary care. The Group noted that private secondary care practitioners would likely be able to access tixagevimab with cilgavimab through a similar mechanism to that of community administration. The Group noted that secondary care specialists would be leading this roll out and considered that communication with these prescribers would be required to allow this to roll out smoothly.

1.16. The Advisory Group considered the collection of information for the use of tixagevimab with cilgavimab for pre-exposure prophylaxis, could include using the National Immunisation Register (NIR) to provide a mechanism for clinicians to record when tixagevimab with cilgavimab had been administered. The Group considered that this should be raised with the Ministry of Health as a formal recommendation.

1.17. The Advisory Group considered the complexity of the prescription and administration of these medicines, particularly in primary care, and the impact that this would have on the delivery of the services. The Group considered that the access to these medicines is complex and would require cross-system effort to reduce inequities.

1.18. The Advisory Group noted that although there are no targets for the number of treatments to be prescribed or administered, an assessment of the impact of the funding criteria on the groups accessing the medicines would be a useful way to assess the success of the criteria and the implementation.

Tocilizumab and baricitinib

1.19. The Advisory Group noted that the tocilizumab supply issue has been resolved. The Group noted that baricitinib was listed on Section H of the Pharmaceutical Schedule in response to the shortage of tocilizumab. The Group considered the ongoing availability of baricitinib for people with severe COVID-19 and the preference of clinicians to use baricitinib over tocilizumab for the inhibitory effect on immune-modulation given the shorter half-life , the increased proportion of hospitalised patients with bacterial co-infection in the current wave of cases, and the ease of oral administration. The Group noted that the use of baricitinib is low for those with severe COVID-19 in the context of Omicron variant infection resulting in lower ICU admissions and previous estimations of use were based on earlier variants.

Eligibility and Access

1.20. The Advisory Group noted that the 75 to 79-year-old group has the highest nirmatrelvir with ritonavir and molnupiravir courses dispensed. The Group noted that the dispensing rates for oral antiviral treatments increase as age increases across all reported ethnicities. The Group noted that there are higher rates of prescribing nirmatrelvir with ritonavir than molnupiravir.

1.21. The Advisory Group noted that the reported dispensing rate was presented as a percentage of those who had reported a positive test to the Ministry of Health. The Group considered that actual usage rates are lower as there would be a group of people who have undiagnosed COVID-19 infection (ie. not tested) or who have not reported their positive test results. The Group considered the impact this has on interpreting the reported dispensing rates and the likely access barriers contributing to this. The Group considered that engagement with this non-testing and/or non-reporting group and with Māori and Pacific communities would be required to

understand how best to improve their current access rates. The Group noted the role of Te Aka Whai Ora in commissioning and operational components of reducing barriers for Māori.

1.22. The Group noted that the dispensing rate in Māori and Pacific peoples, in general, was equivalent to or higher than other ethnicities combined over all age groups except those aged over 100 years.

1.23. The Group considered that data on hospitalisation as a result of COVID-19 infection and those who were treated prior to hospital admission compared to those that were not treated would be useful to gain insights into what impact antiviral treatments were having. The Group noted that Te Whatu Ora is conducting an audit to collect this information.

1.24. The Advisory Group noted estimates of the proportions of the population that were eligible for treatment with oral antivirals. The Group noted that, with the recent widening of access criteria, those over 75 years old were eligible regardless of comorbidities and ethnicity. The Group noted that there was an upward trend in the case dispensing rates (ie "access" rates) within this age group over the four weeks since the wider July criteria were implemented. The Group noted access rates in those aged 65-74 years old, where access rates were higher in Māori and Pacific peoples than other ethnicities combined. However, when comparing access to eligibility for treatment, Māori and Pacific peoples had lower eligibility-adjusted access rates than non-Māori and non-Pacific peoples. The Group noted that in those aged 50-64 years old, access rates again were higher in Māori and Pacific peoples. The Group noted that further information would be provided to them by Pharmac staff after this meeting for further consideration.

Molnupiravir for COVID-19 data update

Application

2.1. The Advisory Group reviewed the updated information for molnupiravir in the treatment of 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 **deferred** its **recommendation** on changing the access criteria until further information is available.

Discussion

Previous consideration of molnupiravir for COVID-19

2.4. Molnupiravir was initially considered for the treatment of mild to moderate COVID-19 at the October 2021 COVID-19 Treatment Advisory Group meeting. The Group recommended molnupiravir be prioritised for treatment of mild to moderate COVID-19 in community and hospital under access criteria targeting identified at risk patient groups. While no clinical benefits had been observed with molnupiravir use in the inpatient setting among patients with moderate-to-severe COVID-19, early initiation of molnupiravir within 5 days of symptom onset in non-hospitalised patients with mild-to-moderate COVID-19 and high risk factors for progression to severe disease has been associated with relative risk reduction of hospitalisation or death by 30% (following initial reports of it providing 50% reductions).

2.4.1. The Advisory Group noted that these clinical trials were conducted prior to the emergence of Omicron variant, and the clinical efficacy of oral antivirals against this currently dominant variant of concern had only been inferred from experimental evidence. Real-world evidence of oral antiviral use in patients with SARS-CoV-2 infection of Omicron variant was lacking.

2.5. Molnupiravir was considered again at the COVID-19 Treatment Advisory Group meeting in April 2022 where the efficacy of funded oral antivirals was re-assessed in the context of the emerging Omicron variant(s). This was then discussed further at the May 2022 meeting. Since the initial outbreak of SARS-CoV-2, a number of variants have emerged with different infectivity profiles, clinical characteristics, and susceptibility to treatments. The Advisory Group noted that at the time the BA.2 subvariant of Omicron was the dominant strain of SARS-CoV-2 in New Zealand. At this time the Advisory Group considered that antiviral treatments molnupiravir retained in-vitro activity against BA.1 and BA.2.

2.5.1. The Group considered that antiviral treatments are likely to retain in-vitro efficacy against current and future variants of SAR-CoV-2 given they target proteins which are well preserved across the variants. The Group considered antiviral treatments are appropriate for use in the general population.

2.6. The Group noted that compared to nirmatrelvir with ritonavir, molnupiravir was expected to be easier to prescribe as it does not have ritonavir's propensity to multiple drug interactions. The Group raised concerns that this could lead to molnupiravir being prescribed by clinicians instead of nirmatrelvir with ritonavir, even though the available initial clinical phase 3 trial data published by Bernal et al 2022 and Hammond et al 2022 indicated that nirmatrelvir with ritonavir reduced the risk of COVID-19 related hospitalisation or death compared to placebo by ~89%, and compared to molnupiravir by ~30% .

Māori Impact

2.7. The Advisory Group noted that prior to the availability of oral antivirals there was proactive action to engage with Māori communities for the administration of remdesivir infusions, specifically within the Auckland region, and considered this service could be re-purposed for those who have a contra-indication to nirmatrelvir with ritonavir. A Member noted that Auckland region has very limited capacity for infusions and little flexibility within that service. The Group noted while the decrease in COVID-19 case numbers and the resulting reduced pressure on the hospitals is positive, the inequity of access for Māori to molnupiravir and nirmatrelvir with ritonavir continues to be of concern given Māori are at higher risk of severe COVID-19 than non-Māori.

Health Need

2.8. The Advisory Group noted that molnupiravir does not target the spike protein, so evolving changes in this protein in emerging and future variants of COVID-19 would not be expected to alter anti-viral activity. The Group noted that molnupiravir has in vitro effect against Omicron variant(s). The Group noted molnupiravir is not Medsafe approved for people under 18 years old and FDA recommends that molnupiravir not be used in those under 18 due to concerns about maturation of bone and cartilage. The Group noted reports that molnupiravir may cause foetal harm, based on animal studies.

2.9. The Advisory Group noted that, like many other treatments for COVID-19, the adverse effect profile of molnupiravir is not well known, due to the novelty of the drug, but nonetheless noted specifically flu-like symptoms, extremity pain, as well as the RNA mutation mechanism having a theoretical effect on the development of new

variants. The Group considered that because of these potential adverse effects that those patients considered for funding should gain a clear benefit from this drug.

2.10. The Advisory Group noted that the earlier a course of molnupiravir was started the better. The Group noted that people treated within 3 days of the start of their symptoms fared better than those that started treatment from day 3 to day 5.

Health Benefit

2.11. The Advisory Group considered that the prior evidence for benefit was reported in unvaccinated people during Delta variant dominance. The Group noted the respective risk of harm between Delta and Omicron variants, where the risk of pneumonitis is lower in Omicron. The Group also noted that those who are vaccinated would be expected to have greater protection against being infected with lower viral loads of SARS-CoV-2; in addition, previous evidence signals that treatment with molnupiravir in people with a low viral load was not superior to placebo.

2.12. The Advisory Group considered a secondary analysis of the MOVe-OUT study (Johnson et al. Ann Intern Med. 2022;175(8):1126-34). The Group noted this was a randomised control trial comparing those who were treated with molnupiravir or placebo and their rates of hospitalisation. The Group noted reported findings of reduced hospitalisation and death through day 29 (Phase 3 all randomised population) compared with placebo (6.8% v 9.7%; 95% CI: 0.1%-5.9%). The Group noted the secondary analysis from this trial reported the frequency of acute care visits (7.2% v 10.6%; RRR 32.1% [CI, 4.4%-51.7%]), COVID-19-related acute care visits (6.6% v 10.0%; RRR 33.8% [CI 5.6%-53.6%]) were less in the molnupiravir treated group. Molnupiravir-treated participants had a decreased need for respiratory interventions compared to placebo-treated participants (RRR 34.3% [95% CI, 4.3%-54.9%]) with similar findings in participants who were hospitalised after randomisation. Participants were not immunised against COVID-19. The Group noted that it was reported that people with a low viral load or who previously had COVID-19 infection did not demonstrate benefit from treatment. The Group noted that in a supplier-provided data update, based on the study above, it was reported that the immunocompromised subgroup included participants with active cancer, HIV, those on immunosuppressant therapies, prior systemic corticosteroid treatment and transplant recipients, and noted other information from the supplier that of those treated with molnupiravir 8.0% were hospitalised or died through day 29 compared to 25% of those in the placebo group (RRR 68%; 95% CI -36.0% to 3.6%).

2.13. The Advisory Group considered evidence from three unpublished cohort studies from Hong Kong provided by the supplier prior to peer review and publication comparing people who were treated with antivirals (molnupiravir and nirmatrelvir with ritonavir) to those who were not:

2.13.1. Wong et al. [Preprint 2022, 13 July posting]
A territory-wide retrospective cohort study assessing the real-world effectiveness of molnupiravir and nirmatrelvir/ritonavir among COVID-19 inpatients during Hong Kong's Omicron BA.2 wave from 26 February to 26 April 2022. Participants were hospitalised patients not requiring oxygen therapy. The study outcomes included a composite outcome of disease progression (all-cause mortality, initiation of invasive mechanical ventilation [IMV], or intensive care unit admission), individual outcomes and lower viral load of cycle threshold value of more than or equal to 30 cycles.

2.13.1.1. In a supplier-provided data update, based on the unpublished study above, it was reported that in the molnupiravir arm of the study a relative risk reduction of 45% and absolute risk reduction of 7.4% with

a number needed to treat of 14 for composite progression outcome cumulatively through to day 30. All-cause mortality was reported at a relative risk reduction of 44% and absolute risk reduction of 7% cumulatively through to day 30.

2.13.2. Wong et al. [Preprint 2022, 26 May]
An unpublished, territory-wide retrospective cohort study assessing the real-world effectiveness of molnupiravir and nirmatrelvir/ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory COVID-19 patients during the BA2.2 wave in Hong Kong from 26 February to 3 May 2022. Investigators reported low vaccination rates in all groups. Based on relative efficacy, this study was supportive of current guidelines prioritising nirmatrelvir/ritonavir use over molnupiravir in community-dwelling COVID-19 patients who are at high risk of hospitalisation or progression to severe disease, should the former be accessible and clinically appropriate.

2.13.3. Yip et al. Clin Infect Dis. [Epub ahead of print 2022, 29 August]
A territory-wide retrospective cohort study considered the impact of the use of oral antivirals agents on the risk of hospitalisation in community COVID-19 patients. Non-hospitalised COVID-19 patients who attended designated outpatient clinics between 16 February and 31 March 2021 were identified. The primary endpoint was hospitalisation. The secondary endpoint was a composite of intensive care unit admission, invasive mechanical ventilation use, and/or death. Of 93,883 patients, 83,154 (88.6%), 5,808 (6.2%), and 4,921 (5.2%) were oral antiviral non-users, molnupiravir users, and nirmatrelvir/ritonavir users respectively. The complete vaccination rate was reported as 36.1% for molnupiravir treated, 42.6% nirmatrelvir with ritonavir treated and 55.9% antiviral non-users. Compared to non-users, oral antiviral users were older and had more comorbidities, lower complete vaccination rate, and more hospitalisations in the previous year. Molnupiravir users were older, and had more comorbidities, lower complete vaccination rates, and more hospitalisations in the previous year than nirmatrelvir/ritonavir users. At a median follow-up of 30 days, 1,931 (2.1%) patients were admitted to hospital and 225 (0.2%) patients developed the secondary endpoint (composite of intensive care unit admission, invasive ventilation use and death). After propensity score weighting, molnupiravir use (weighted hazard ratio 1·17, 95% CI 0·99-1·39, *P*=0·062) was not associated with a reduced risk of hospitalisation than non-users. The use of molnupiravir was not associated with a lower risk of the secondary endpoint as compared to non-users. In the subgroup of patients aged ≥60 years or aged <60 years with comorbidities, molnupiravir use was not associated with a reduced risk of hospitalisation than non-users.

2.14. The Advisory Group considered the level of confounding by indication in real-world retrospective cohort studies, makes determining a valid comparator group more difficult, as it is likely those treated with antivirals in the real world setting are at higher risk of severe disease than those in the randomised controlled clinical trials. The Group considered that the available information on the methods used to adjust for this confounding was not clear. The Group noted that when measuring for differences in initiation of invasive mechanical ventilation and admission to ICU outcomes in hospital inpatients with COVID-19 (Wong et al. July 2022) and in the risk of hospitalisation in people attending COVID-19 outpatient clinics (Yip et al. 2022) that molnupiravir did not appear to be superior to placebo. The Group considered that nirmatrelvir with ritonavir was probably superior to molnupiravir based on the unpublished data presented but noted that these comparisons are not based on head-to-head direct comparison trials. The Group considered that the adjustment for confounding within each of these studies was not clear and this reduced the value of

this data at the current time. The Group also considered the vaccination rate in the populations assessed (Wong et al. May 2022, Yip et al. 2022), noting that higher vaccination rates were associated with lower death rates overall, consequently the absolute reduction in deaths was relatively small in both molnupiravir and nirmatrelvir with ritonavir treatment groups in the context of the currently dominant Omicron variant of COVID-19.

2.15. The Advisory Group considered that this new information relating to molnupiravir re-enforces that nirmatrelvir with ritonavir has reported likely higher efficacy compared to molnupiravir. The Group considered that the unpublished data provided could be confounded by indication due to differences in baseline risk of people being selected for treatment. The Group considered that this confounding was adjusted for by propensity analysis but was not able to interpret the extent this adequately controlled for known and unknown confounders. The Group considered it is unlikely treatment with molnupiravir would significantly prevent severe acute COVID-19 lung disease in the current context of low incidence and prevalence in a predominantly Omicron variant of COVID-19 in New Zealand.

2.16. The Advisory Group noted the published results of a randomised control trial examining the efficacy and safety of molnupiravir against Omicron variant infection (Zhou et al. Front Pharmacol. 2022). The primary endpoint was time to viral RNA clearance (9 days vs 10 days median, *P*=<0.01) and at day 10 of the molnupiravir treated group 76.3% were returning a negative PCR test compared to the placebo group returning 51.6% negative (*P*=0.02). The Group noted that there was no statistically significant difference between the clinical outcomes of the molnupiravir and placebo group.

2.17. The Advisory Group considered that to justify the use of molnupiravir the patient would need a high risk of severe disease. The Advisory Group considered that the current access criteria for molnupiravir were likely allowing it to be prescribed to people that may have several risk factors but are not high-risk enough to receive benefit from treatment. The Group considered the targeting of access to these high-risk people who are not able to take nirmatrelvir with ritonavir would likely be of benefit.

2.18. The Group noted that a hierarchy for COVID-19 treatments could be included within community and hospital guidelines. The Group considered that changing the access criteria specifically for molnupiravir to target treatment to the highest risk people was less likely to be effective compared to changing prescribing guidelines.

2.19. The Advisory Group considered results from an unpublished retrospective observational study provided by the supplier investigating the prevalence of people who are taking medications with potential interactions with nirmatrelvir with ritonavir). It was reported that there was a 60% prevalence of potential severe to moderate drug interactions with nirmatrelvir with ritonavir. The Group noted that they had previously estimated this as 30-40% of eligible patients in New Zealand. The Group noted that drug interactions were assessed against the Liverpool DDI checker, Paxlovid US FDA factsheet and Lexicomp database to give an overall rating of low to severe interaction. The Group considered that it was unclear as to the clinical significance of these interactions and that an unknown proportion of these interactions could be mitigated to allow these people to receive nirmatrelvir with ritonavir.

2.20. The Group considered the COVID-19 environment in New Zealand compared to the rest of the world. The Group noted that New Zealand has a high risk, COVID-19 naïve population compared to other populations that have not used the same strategies to control case numbers as New Zealand has. The Group noted that the United Kingdom is likely to have a different level of immunity due to differences in the incidence and prevalence of COVID-19 over the last 3 years. On this basis, the

Group considered the potential effects of this limiting the relevance of any findings to the New Zealand population, particularly those who are not vaccinated and have not had an infection. The Group considered that potentially some benefit, at least for a short period, could be assumed as New Zealand moves toward an endemic phase. The Group noted that the current dominant Omicron subvariant was less virulent compared to previously dominant variants of COVID-19, so considered that extrapolation from emerging evidence was difficult when accounting for variant evolution and differences in severity of symptoms. The Group noted the COVID-19 mortality rate in New Zealand was estimated as 1 in 1000 cases. Given this, it was considered that due to the low risk of death overall that use of molnupiravir should be targeted and confined to those with a higher risk of severe disease, as the risk of side-effects in people of lower risk would out-weigh the potential benefit.

2.21. The Advisory Group considered the potential negative implications of narrowing and restricting the access criteria for molnupiravir to those who have are higher risk of severe disease, with a risk that this may result in molnupiravir being misconstrued to be a preferred option for these high-risk people. The Group considered there are two funded and readily available alternatives (nirmatrelvir with ritonavir, and remdesivir) and that the current evidence indicates these are likely more effective than molnupiravir in the current Omicron environment. The Group noted that there are no direct head-to-head trials directly comparing antiviral treatments for COVID-19.

2.22. The Advisory Group considered the barriers to prescribing nirmatrelvir with ritonavir over molnupiravir. The Group considered that more information relating to this was required from prescribers to fully assess the impact the access criteria may have on clinical decision making. The Group considered that there could be a bias towards molnupiravir as it does not have the complex drug interactions characteristics of nirmatrelvir with ritonavir. The Group considered whether funding and capacity in primary care is enough to support the prescribing of this drug given the time it would take to assess the interactions. The Group considered that reducing these barriers, such as confidence in prescribing nirmatrelvir with ritonavir and how to mitigate the potential interactions, and being resourced to either have the time to assess or have clinical support doing so (eg locally available clinical pharmacists) would likely encourage the prescribing of nirmatrelvir with ritonavir over molnupiravir.

2.23. The Advisory Group considered the use of prescriber education as a tool to increase the prescribing of nirmatrelvir with ritonavir compared to molnupiravir for eligible people. The Group considered that the likely barrier is the time it takes to assess the potential drug interactions given the target population is likely receiving medicines (often many) for co-morbidities. The Group noted that there is no tangible information as to the barriers faced by primary care in the prescribing of nirmatrelvir with ritonavir.

2.24. The Group noted that the temporary reclassification of nirmatrelvir with ritonavir and molnupiravir to ‘Pharmacist Only’ medicines allows the burden of assessment of interactions to be shared between GP’s and pharmacists. The Group noted the differences between pharmacist prescribers and those in General Practice. The Group noted that initial data for rates of prescribing molnupiravir by these two groups are similar. The Group noted that this would continue to be monitored.

2.25. The Advisory Group noted while the decrease in case numbers and reduced pressure on the hospitals from COVID-19 is positive, the inequity of access for Māori and Pacific peoples to molnupiravir and nirmatrelvir with ritonavir continues to be of concern given they are at higher risk of more severe disease than non-Māori non-Pacific people. The Group considered that access criteria differentiating nirmatrelvir with ritonavir and molnupiravir by widening access specifically to nirmatrelvir with ritonavir would be more desirable, as restricting access to molnupiravir is likely unacceptable to the public and could limit access to some people who might

otherwise benefit. The Group noted that prior to the availability of nirmatrelvir with ritonavir and molnupiravir there was proactive action to engage well with Māori and Pacific communities, specifically within the Auckland region, to increase the administration of remdesivir infusions for these communities. The Group considered this service could be re-purposed for those who have a contraindication to nirmatrelvir with ritonavir.

2.26. The Advisory Group considered that it would be beneficial to formulate clinical guidance to encourage prescribers to prescribe nirmatrelvir with ritonavir and remdesivir in preference to molnupiravir. The Group noted that Pharmac's role is not a supplier of clinical information but suggested collaboration with Te Whatu Ora and Te Aka Whai Ora to support the development of guidance.

2.27. The Advisory Group considered that the information presented was not sufficient to recommend a change to the current access criteria. The Group considered that further information was required including data on deaths from COVID-19 associated illness, information on those who received funded COVID-19 treatments prior to hospitalisation, and further dispensing data. The Group considered that nirmatrelvir with ritonavir prescribing should be encouraged over molnupiravir prescribing. The Group also recommended that collaboration with Te Whatu Ora be used to facilitate increased access.

2.28. The Advisory Group noted the PANORAMIC clinical study, which was evaluating the effectiveness of molnupiravir in preventing hospitalisation or death from of COVID-19 compared to standard of care, had recently stopped recruitment. The Advisory Group considered that it would be useful for it to review the results of the study once they are available, noting it would provide data for molnupiravir in the treatment of the Omicron variant of COVID-19.

Tixagevimab with cilgavimab for the treatment of COVID-19

Interests

1.1. The Advisory Group reported no conflicts of interest with regard to this agenda item.

Application

1.2. The Advisory Group reviewed the access criteria for tixagevimab with cilgavimab in the treatment of COVID-19.

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

Recommendation

1.4. The Advisory Group recommended that tixagevimab with cilgavimab for the treatment of early COVID-19 with no new oxygen requirement (community) be subject to the following Access Criteria:

Indication – Treatment of early COVID-19 with no new oxygen requirement
Any relevant practitioner. Approvals valid for 1 week for all applications meeting the following criteria:
All of the following:

1. Patient has not had tixagevimab with cilgavimab in the last 6 months; **AND**
2. Patient has confirmed (or probable) symptomatic COVID-19; **AND**
3. Patient does not require supplemental oxygen # **AND**
4. Either:

4.1. Patient is severely immunocompromised and considered to be at risk of inadequate immune response to SARS-CoV-2 vaccination or infection due to **ANY** of the following clinical situations:

- heart or lung transplant recipient (any time frame)
- other solid-organ transplant recipient with any of the following:
  - transplant received within the last 12 months
  - receiving induction immunosuppressant treatment (any timeframe)
  - receiving maintenance immunosuppressant treatment that includes mycophenolate mofetil (any timeframe)
  - treated for graft rejection within the past 12 months
- allogenic haematopoietic stem cell transplant recipient with any of the following:
  - transplant received within last 12 months
  - has chronic graft versus host disease
  - requires significant ongoing immunosuppression for another reason
- autologous haematopoietic stem cell transplant received within the last 12 months
- multiple myeloma on active and/or maintenance treatment
- combined primary immunodeficiency syndromes (including Severe Combined Immunodeficiency (SCID))
- common variable immunodeficiency (CVID) with additional T-cell defects, past opportunistic infection or requiring immunosuppressive therapy
- diagnosed humoral immunodeficiency with baseline IgG < 3g/L
- HIV with a CD4 T lymphocyte cell count <200 cells/mm3
- person who is receiving:
  - potent B-cell or T-cell depleting therapy within the previous 12 months or planned to receive within two weeks of tixagevimab and cilgavimab administration*
  - a B-cell inhibitor (eg. venetoclax or a Bruton tyrosine kinase inhibitor)
  - ruxolitinib
  - regular 3-4-weekly intravenous or subcutaneous immunoglobulin
  - sphingosine 1- phosphate receptor modulator therapy (eg fingolimod) within previous 12 months
  - high dose cyclophosphamide (>1g/m2) within previous 6 months.

- History of previous persistent SARS-CoV-2 infection (defined as a laboratory confirmed diagnosis of persistent SARS-CoV-2 infection persisting ≥20 days) that has since resolved;

OR

1.2 Person is both:

- not able to be vaccinated against COVID-19 due to medical contraindication (for example a history of severe adverse reaction to a COVID-19 vaccine or its components) **AND**
- is considered at high risk of severe illness from COVID-19 infection.

Notes:
* potent B-cell or T-cell depleting therapy such as rituximab, obinutuzumab, ocrelizumab, bendamustine, fludarabine, cladribine, alemtuzumab, anti-thymocyte globulin, CamPath antibody treatment, anti-B-cell bispecific antibody, CAR T-cells or BiTE antibody treatment

Supplemental oxygen to maintain oxygen saturation >93% or at or above baseline for patients with chronic resting hypoxia

1.5. The Advisory Group **recommended** that tixagevimab with cilgavimab for the treatment of COVID-19 with new oxygen requirement (hospital) be subject to the following Access Criteria:

Indication – Treatment of early COVID-19 with new oxygen requirement
Any relevant practitioner. Approvals valid for 1 week for all applications meeting the following criteria:
All of the following:

1. Patient has not had tixagevimab with cilgavimab in the last 6 months; **AND**
2. Patient has confirmed (or probable) symptomatic COVID-19; **AND**
3. Either:
   3.1. Patient does require supplemental oxygen (to maintain oxygen saturation >93%); **OR**
   3.2. Patient does require supplemental oxygen to maintain oxygen saturations no lower than baseline (for patients with chronic resting hypoxia); **AND**
4. Either:
   4.1. Patient is severely immunocompromised and considered to be at risk of inadequate immune response to SARS-CoV-2 vaccination or infection due to **ANY** of the following clinical situations:
   - heart or lung transplant recipient (any time frame)
   - other solid-organ transplant recipient with any of the following:
     - transplant received within the last 12 months
     - receiving induction immunosuppressant treatment (any timeframe)
     - receiving maintenance immunosuppressant treatment that includes mycophenolate mofetil (any timeframe)
     - treated for graft rejection within the past 12 months
   - allogenic haematopoietic stem cell transplant recipient with any of the following:
     - transplant received within last 12 months
     - has chronic graft versus host disease
     - requires significant ongoing immunosuppression for another reason
   - autologous haematopoietic stem cell transplant received within the last 12 months
   - multiple myeloma on active and/or maintenance treatment
   - combined primary immunodeficiency syndromes (including Severe Combined Immunodeficiency (SCID))
   - common variable immunodeficiency (CVID) with additional T-cell defects, past opportunistic infection or requiring immunosuppressive therapy
   - diagnosed humoral immunodeficiency with baseline IgG < 3g/L
   - HIV with a CD4 T lymphocyte cell count <200 cells/mm3
   - person who is receiving:
     - potent B-cell or T-cell depleting therapy within the previous 12 months or planned to receive within two weeks of tixagevimab and cilgavimab administration*
     - a B-cell inhibitor (eg venetoclax or a Bruton tyrosine kinase inhibitor)
     - ruxolitinib
     - regular 3-4-weekly intravenous or subcutaneous immunoglobulin
     - sphingosine 1- phosphate receptor modulator therapy (eg fingolimod) within previous 12 months
     - high dose cyclophosphamide (>1g/m2) within previous 6 months.

- History of previous persistent SARS-CoV-2 infection (defined as a laboratory confirmed diagnosis of persistent SARS-CoV-2 infection persisting ≥20 days) that has since resolved

OR

4.2. Person is both:

- not able to be vaccinated against COVID-19 due to medical contraindication (for example a history of severe adverse reaction to a COVID-19 vaccine or its components) **AND**
- is considered at high risk of severe illness from COVID-19 infection.

Notes:
* potent B-cell or T-cell depleting therapy such as rituximab, obinutuzumab, ocrelizumab, bendamustine, fludarabine, cladribine, alemtuzumab, anti-thymocyte globulin, CamPath antibody treatment, anti-B-cell bispecific antibody, CAR T-cells or BiTE antibody treatment

1.6. The Advisory Group considered the following when making these recommendations:

- people previously considered in the pre-exposure prophylaxis access criteria are the most at risk of severe disease and death
- removing the restriction of treatment to less than 7 days for those being treated in community and less than 12 days for those in hospital, to encourage earlier administration
- exclusion of reference in hospital and community access criteria to treatment with adjuvant remdesivir or other agents, to give the clinician discretion over combination use.

1.7. The Advisory Group **deferred** its recommendation for tixagevimab with cilgavimab for the treatment of early COVID-19 with no new oxygen requirement, in those contraindicated to nirmatrelvir with ritonavir, until more information was available.

1.8. The Advisory Group noted that its recommendations are made based on available evidence at a fixed point in time and may become superseded and require review as the COVID-19 pandemic continues to evolve and new variants emerge, which may affect the effectiveness of available treatments.

Acknowledgement

1.9. 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

1.10. The Advisory Group considered that barriers to accessing treatment services place an additional burden on Māori. The Group considered the roles of the Te Aka Whai Ora - Māori Health Authority, Manatū Hauora - Ministry of Health and Te Whatu Ora - Health NZ in reducing the access barriers to COVID-19 treatments, and recommended that they should ensure sufficient support is provided to enable access for Māori. The Group acknowledged that Māori are at a higher risk of developing severe disease and death than non-Māori. The Group noted the differences between primary and secondary care and that some secondary care specialists had begun identifying people who are eligible for pre-exposure prophylaxis with tixagevimab with cilgavimab. The Group also noted that within specialist services, such as transplant services, Māori were overrepresented than compared with the general population.

Pacific peoples impact

1.11. The Advisory Group considered that barriers to accessing treatment services place an additional burden on Pacific peoples compared to non-Pacific peoples. The Group noted the differences between primary and secondary care. The Group considered Pharmac should engage with the Care in the Community team at Te Whatu Ora to enable equitable access through the community within the constraints of the supply available.

Previous consideration of tixagevimab with cilgavimab (Evusheld) for treatment of COVID-19

1.12. Tixagevimab with cilgavimab for the treatment of COVID-19 was initially considered at the December 2021 meeting of the COVID-19 Treatments Advisory Group. At this meeting the Advisory Group recommended access criteria for tixagevimab with cilgavimab in the treatment of COVID-19 for people with mild to moderate COVID-19. At the time, the Advisory Group recommended that the access criteria should be similar to the criteria for casirivimab with imdevimab (Ronapreve) on the basis of the similar patient populations being targeted by the treatments. Tixagevimab with cilgavimab for the treatment of COVID-19 was considered again at the April 2022 meeting. Since the initial outbreak of COVID-19, a number of SARS-CoV-2 variants have emerged with different infectivity profiles, clinical characteristics, and susceptibility to treatments. The Advisory Group noted that at the time the BA.2 subvariant of Omicron was the dominant strain of SARS-CoV-2 in New Zealand. It was noted that cilgavimab but not tixagevimab was shown to maintain serum neutralisation activity against Omicron BA.1 and BA.2 subvariants. Tixagevimab used in combination with cilgavimab did not offer additional neutralisation benefits. Currently the BA.4 and 5 strains are the dominant subvariants of SARS-CoV-2 in New Zealand (Ministry of Health, SARS-CoV-2 Variants of Concern, page 10: accessed 17 August 2022). It was considered there was potential for tixagevimab with cilgavimab to be used in combination with antiviral agents in profoundly immunocompromised patients, if infected with a susceptible variant. Of the groups considered, the Advisory Group considered those people at the highest risk of severe disease to be:

- those who are severely immunocompromised as defined by Ministry of Health (updated 15 July 2022)
- solid organ transplant recipients including lung, liver and kidney with specific reference to those taking mycophenolate at a dose of one gram or more
- those on treatment for haematological malignancy
- those receiving anti-CD20 or B-cell depleting therapies.

1.13. It was noted that one week following administration, tixagevimab with cilgavimab conferred neutralising antibody concentrations approximately 22-fold greater than those associated with convalescent serum (Levin et al. N Engl J Med 2022; 386:2188-200). Data from the PROVENT Phase III Trial suggested that prophylactic treatment with tixagevimab with cilgavimab could provide protection from COVID-19 infection for at least 6 months following administration. The Advisory Group considered these long-lasting effects from a single dose of tixagevimab and cilgavimab could be an advantage when treating underserved populations such as Māori and Pacific peoples.

1.14. The Advisory Group noted that at the time of the April 2022 meeting the Group did not make any further recommendations for tixagevimab with cilgavimab in the treatment of COVID-19. It was also noted that from the available information that generally the treatment was safe and well tolerated but that there was a possible signal for cardiovascular risk noted by FDA EUA and a risk of haematoma in haematology patients if the patient was anticoagulated or had thrombocytopenia.

Health Benefit

1.15. The Advisory Group reviewed summarised results for monoclonal antibodies other than tixagevimab with cilgavimab in the treatment of COVID-19 as early treatment of COVID-19 in the community and in people hospitalised from COVID-19 infection. The Advisory Group noted that trials of different monoclonal antibodies in the early treatment of COVID-19 in community settings were conducted in similar populations and reported similar results, namely that in high risk, unvaccinated people, early treatment with a monoclonal antibody that is effective against the circulating variant may reduce risk of hospitalisation or severe illness from COVID-19 infection.

1.16. The Advisory Group considered evidence for the effectiveness of monoclonal antibodies in the treatment of people hospitalised with COVID-19 and noted there were very few trials undertaken and publications available for monoclonal antibodies in this setting.

1.16.1. The Group noted that casirivimab with imdevimab showed reduced mortality but only in seronegative people as shown in the RECOVERY trial (RECOVERY Collaborative Group. Lancet. 2022;399:665-76.) including those who have received a full vaccination course but had not mounted an adequate immune response, The Advisory Group noted that casirivimab with imdevimab was available in New Zealand for the treatment of COVID-19 but only very small volumes had been used, as available evidence suggested it was not effective against the Omicron variant of SARS-CoV-2, including currently circulating subvariants.

1.16.2. The Group also noted based on available evidence, sotrovimab did not demonstrate any benefit in people hospitalised with COVID-19, regardless of serostatus. The Group noted that sotrovimab is currently not available for use in New Zealand.

1.17. The Advisory Group considered that if every unvaccinated person with risk factors for severe COVID-19 was included in the Access Criteria then this would be a large group (estimated >100,000 people) who may or may not benefit. The Group considered those that would benefit most from treatment would be the same group included in the pre-exposure prophylaxis criteria. The Group was unable to, based on current information, estimate the size of this group.

1.18. The Advisory Group noted that currently tixagevimab with cilgavimab is funded for pre-exposure prophylaxis to COVID-19 in high-risk people under Pharmac Access criteria. The Advisory Group considered that if those included in the pre-exposure prophylaxis criteria have had a prophylactic dose then most of the high-risk group would be protected against COVID-19 infection. Regarding what proportion of people would need to be re-dosed in six months following the administration of tixagevimab with cilgavimab, the

Group considered that if given to those that meet the pre-exposure prophylaxis criteria, regardless of whether it is given as a treatment or prophylactically, all would need to be re-dosed if the dominant variant(s) at that time were still susceptible to tixagevimab with cilgavimab.

1.19. The Advisory Group noted that people included in the recommended Access Criteria could, alternatively, be treated with high titre convalescent plasma. The Group noted that currently the information supporting this use is mixed. The Group noted trials using convalescent plasma in hospitalised people are limited. REMAP-CAPAngus DC et al. Ann Am Thorac Soc. 2020;17:879-91) reported no benefit to those people with COVID-19 who require organ support in an intensive care unit but tixagevimab with cilgavimab remains an option as benefits outweigh adverse effects. The Group noted that the likely mechanism of action is through neutralisation of the virus similar to monoclonal antibody action and efficacy.

1.20. The Advisory Group considered available evidence for tixagevimab with cilgavimab in the treatment of COVID-19.

1.20.1. The Group noted the TACKLE study (Montgomeryet al. Lancet Respir Med. [Epub ahead of print] 2022), where participants were given 600 mg of tixagevimab with cilgavimab via intramuscular injection in the community. The Group noted that the population included were younger adults, with a median duration of symptoms of 5 days who were unvaccinated, with few previously been infected, and 5% of participants were immunocompromised. The Group noted this study was carried out when the dominant variant was the Delta variant. The Group noted that those treated earlier had the most benefit. The Group noted that there was a reported decrease in severe illness in those treated with tixagevimab with cilgavimab compared to those given placebo. The Group noted that based on the result of the trial treatment with tixagevimab with cilgavimab did not appear to reduce mortality.

1.20.2. The Group considered that the results of the TACKLE study were similar to the results reported for other monoclonal antibodies in the treatment of COVID-19.

1.20.3. The Group noted the ACTIV-3/TICO study (Ginde et al. Lancet Respir Med. [Epub ahead of print] 2022) was conducted in hospitalised patients during the Delta variant dominance and low rates of vaccination. The Group also noted that the standard of care in this study included remdesivir and steroids for pneumonitis (75% of participants). In addition, the Group noted that the study excluded people receiving invasive mechanical ventilation. The Group noted that the study reported that the primary outcome of sustained clinical recovery (14 days at home post-hospitalisation) was not reached. Of those included in this study 10% were immunocompromised including 5-6% who were on anti-rejection medicines, and 75% were unvaccinated.

1.20.4. The Group noted that the ACTIV-3/TICO study did not report a benefit in the proportion of people achieving sustained clinical recovery between people receiving tixagevimab with cilgavimab and people receiving placebo (89% for tixagevimab with cilgavimab and 86% for placebo, p=0.21), however treatment

with tixagevimab cilgavimab was associated with lower mortality (9% for tixagevimab with cilgavimab compared to 12% for placebo, p=0.032).

1.21. The Advisory Group considered the evidence of benefit for those who are immunocompromised to be of very low strength and of low to moderate strength for the general population and considered the quality of the evidence to be moderate to high. The Advisory Group considered that the environment that these studies were conducted in is not reflective of the current New Zealand COVID-19 environment where the Omicron BA.5 variant is dominant, and a significant proportion of the general population is vaccinated (>90% of over 12-year-olds; Ministry of Health website, accessed 1 September 2022). The Group considered that evidence for use of tixagevimab with cilgavimab in high-risk patients and those likely to have an immune response to be limited.

1.22. The Advisory Group considered the lack of evidence for treatment with tixagevimab with cilgavimab for efficacy in Omicron BA.5. The Group considered the rate of variant evolution is unknown and that any recommendations on efficacy made would not be able to be extrapolated to future emerging variants. The Group considered the benefit of this treatment is limited to variants where tixagevimab with cilgavimab has adequate neutralising effect. The Group considered that the evidence for efficacy in Omicron BA.5 is lacking but *in vitro* laboratory data is supportive. The Group considered the neutralisation titre in Omicron BA.2 as shown in a study of those who received kidney transplants (Bertrand et al. Kidney Int, 2022;102:440-42) and the neutralisation of BA.5 is shown to be within the same range for tixagevimab with cilgavimab in *in vitro* studies (Touret et al. Sci Rep. 2022;12:12609) The Group considered that although there are no *in vivo* studies of tixagevimab with cilgavimab in Omicron BA.5, it plausible that tixagevimab with cilgavimab would have efficacy against Omicron BA.5.

1.23. The Advisory Group considered the benefit of tixagevimab with cilgavimab for treatment of COVID-19 in the context of Omicron BA.5. The Group considered that there was no comparative data with other treatments but tixagevimab with cilgavimab has a potential passive immunity effect after use in COVID-19 treatment as reported in STORM CHASER trial (Levin et al. Clin Infect Dis. 2022:ciac899). The Group considered that tixagevimab with cilgavimab was generally well-tolerated with no drug-drug interactions and the most common side effect being injection site reactions.

1.24. The Advisory Group considered the additional benefits to family whānau or wider society. The Group considered it could be assumed that the additional benefits would be similar to other COVID-19 treatments but with the potential pre-exposure prophylaxis coverage for future exposure to susceptible variants so reducing the risk of bring the virus into the home and transmitting it to other household members or requiring isolation.

1.25. The Advisory Group considered the administration of tixagevimab with cilgavimab and the impacts on the health system. The Group considered that the administration of intramuscular or intravenous injections could increase the pressure on the health system as there is limited capacity to give intravenous injections to people with COVID-19 in the community when compared to oral antiviral treatments that can be prescribed and dispensed via non-contact mechanisms.

1.26. The Advisory Group further considered the delivery of tixagevimab with cilgavimab in the community. It was noted that tixagevimab with cilgavimab given intravenously has a higher initial bioavailability over the first three days after administration than intramuscular but evidence for clinical relevance of this is lacking. The Group considered that earlier administration (<3 days after symptom onset) of tixagevimab with cilgavimab was associated with greater reductions in risk of developing severe COVID-19 compared to later administration (>5 days after symptom onset). The Group however considered that this would be resource intensive, as there would likely be few people who are able to administer intravenous injections in the community. The Group considered that there is unlikely to be sufficient capacity to meet the needs in the current or proposed setting. It was also noted that it was likely that there would be significant disparities in the ability to deliver this service across the country.

1.27. The Advisory Group noted other authorities' approach to the use of tixagevimab with cilgavimab for treatment of COVID-19. The Group noted that Australian guidelines (Australian guidelines for the clinical care of people with COVID-19. Published 2022-08-18 (v62.1)) suggest that tixagevimab with cilgavimab be considered for treatment of COVID-19. The Group noted that the British guidelines have not included the use of tixagevimab with cilgavimab for the treatment of COVID-19 (NICE COVID-19 rapid guideline: Managing COVID-19). The Group noted the different COVID-19 environments in these different jurisdictions.

1.28. The Advisory Group considered people who are contraindicated to nirmatrelvir with ritonavir and that the addition of criteria would allow them to access tixagevimab with cilgavimab for treatment of COVID-19 as an alternative. The Advisory Group noted currently available evidence that indicated that tixagevimab with cilgavimab may be a more effective treatment than other available oral antiviral treatments (molnupiravir) (Montgomery et al. Lancet Respir Med. [Epub ahead of print] 2022; Levin et al. N Engl J Med. 2022;386(23):2188-200; Bernal et al. N Engl J Med. 2022; 386:509-20), and a single intramuscular dose of tixagevimab with cilgavimab may offer a simpler alternative in the community setting to having a three-day course of intravenous remdesivir. The Group considered that this would increase the size of the eligible population substantially, given that interactions with nirmatrelvir with ritonavir are not uncommon. The Group was not able to estimate the size of this group.

1.28.1. The Group noted that the evidence for use of tixagevimab with cilgavimab in those who are contraindicated to nirmatrelvir with ritonavir is not readily available, and use in this setting would rely on extrapolating evidence, with the potential to result in funding to a large number of people with unknown benefit.

1.29. The Advisory Group noted that there is no trial using tixagevimab with cilgavimab in a vaccinated cohort with symptomatic COVID-19 and it is unclear if a vaccinated person who is not immunosuppressed would benefit from passive immunity. The Group considered that there was not enough information on group size or efficacy in this group to make a recommendation at this time, and the access criteria could be reviewed on receipt of this information.

1.30. The Advisory Group noted that in a study of people who received renal transplants, all participants were vaccinated and (Bertrand et al. Kidney Int, 2022;102:440-2) those that did not respond to vaccination, defined as more than 264 antibody binding units, benefitted from tixagevimab with cilgavimab. The Group noted that this group benefitted no more from treatment with tixagevimab with cilgavimab than they would have had they responded to vaccination against COVID-19. Based on this, The Advisory Group considered that those people who did not mount a sufficient immune response to vaccination, or who were unable to be vaccinated for clinical reasons and so have no neutralising titre, would benefit from tixagevimab with cilgavimab.

Suitability

1.31. The Advisory Group considered the dose given via either intramuscular or intravenous should be 300 mg of each antibody; tixagevimab and cilgavimab (600mg total) in the context of BA.5 as in the TACKLE trial (Ginde et al. Lancet Respir Med. [Epub ahead of print] 2022).

1.32. The Advisory Group noted that tixagevimab with cilgavimab is able to be given via an intramuscular or intravenous injection. It was noted that administration via intramuscular injection had injection site pain as an adverse effect. It was considered that this is less likely to be an issue with intravenous administration.

1.33. The Advisory Group considered that the administration of tixagevimab with cilgavimab via intravenous injection delivers a higher serum concentration initially compared to intramuscular injection. The Group considered however that both methods of administration then sustain similar mean serum concentrations (AUC) over three days. The Group considered that there is a lack of evidence that delivery by either route gave better clinical outcomes.

1.34. The Advisory Group considered the risk of bleeding of the group considered for funding. It was considered that these people would be more likely to have low or non-functioning platelets or coagulopathies that would put them at a higher risk of bleeding on IM administration. The Group considered that in practice this is uncommon.

Funding criteria

1.35. The Advisory Group considered that the indication of early disease in community should be under the same criteria as pre-exposure prophylaxis and noted the suggested restriction of treatment of those who have been symptomatic for less than 7 days. The Group considered that there should be emphasis on early administration regardless of the time restriction within the criteria. The Group was supportive of removing the restriction of treatment of those who have been symptomatic for less than 7 days. The Group considered that the role of pre-exposure prophylaxis be emphasised for the high-risk group. The Group considered that given the limited stock that treatment should be targeted to those included in the pre-exposure prophylaxis but have not yet received a dose for prophylaxis.

1.36. The Advisory Group considered that for those with COVID-19 in hospital that the restriction to people who have been symptomatic for less than 12 days be removed and that there should be no restriction on the use of this agent with other antivirals. The

Group considered the use of additional agents should at the physician's discretion, according to the guidelines and evidence for efficacy available at the time. The Group considered that those who aren't able to get the prophylactic dose prior to COVID-19 infection should be able to receive a dose upon presentation to hospital.

1.37. The Advisory Group noted that this will be listed on the Pharmaceutical Schedule with an endorsement linked to the access criteria on the Pharmac website. It was noted that this was to allow flexibility for changes to access criteria but means that data on which indication is accessed under is not available.