Record of the COVID Treatments Advisory Group Meeting held on 14 April 2022

The role of Advisory Groups and records of meetings

Note that this document is not necessarily a complete record of the COVID Treatments Advisory Group meeting; only the relevant portions of the meeting record relating to COVID Treatments Advisory Group discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

The COVID Treatments Advisory Group may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule; or

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule; or

(d) recommend that Pharmac discontinue funding of a pharmaceutical currently on the Pharmaceutical Schedule.

Advisory Groups give advice to Pharmac, including recommendations', based on the Groups' different, if complementary, roles, expertise, experience, and perspectives. Recommendations made by the COVID-19 treatments Advisory Group are in the context of COVID-19 treatments only. Pharmac is not bound to follow the recommendations made below.

The record of this Advisory Group meeting will be reviewed by PTAC at an upcoming meeting.

Attendance

Present
Chair – Dr Jane Thomas
Eamon Duffy
Dr Gillian Hood
Dr Graham Mills
Dr Justin Travers
Dr Nigel Raymond
Dr Robyn Manuel
Professor Stephen Munn

Apologies
Professor Brian Anderson
Dr Kerry Benson-Cooper
Dr Jessica Keepa
Associate Professor Marius Rademaker
Dr Tim Cutfield

1. Pharmac Update

Discussion

1.1. 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.

1.2. The Advisory Group noted that nirmatrelvir with ritonavir (Paxlovid) was now available in the community and that the COVID care in the community team at Te Whatu Ora were working with Pharmac to facilitate the implementation of this. The Group noted that feedback was received in response to the release of the access criteria for antiviral treatments and in response to the sector requesting availability of the oral treatments in Te Whatu Ora Hospitals the Group noted these were expected to be available from late April 2022.

1.3. The Advisory Group noted that at the time of the meeting molnupiravir was not Medsafe approved but would be distributed under the same arrangement as nirmatrelvir with ritonavir once it was available. The Group noted that the stock was yet to arrive in New Zealand.

1.4. The Advisory Group noted that the agreement for tixagevimab with cilgavimab (Evusheld) for 20,000 courses had been approved but Evusheld was not Medsafe approved. The Group noted that tixagevimab with cilgavimab was expected to be available from mid-2022 and would require further advice on the access criteria which had been previously discussed by the Group.

1.5. The Advisory Group noted that supplier negotiations for supply of sotrovimab (a monoclonal antibody treatment) had concluded and clinical advice is required to assess the group that is most likely to benefit from treatment. The Group noted that this would be

announced after receiving clinical advice and would likely be included in the same consultation as access criteria for tixagevimab with cilgavimab.

1.6. The Advisory Group noted that further advice would be sought regarding the access criteria and SARS-CoV-2 variants of concern as evidence becomes available.

Sotrovimab for the treatment of COVID-19

1. Application

1.1. The Advisory Group considered material provided by the Supplier and Pharmac staff regarding sotrovimab for the treatment of COVID-19. The Advisory Group took into account, where applicable, Pharmac's relevant decision-making framework when considering this item.

2. Recommendation

2.1. The Advisory Group **recommended** that sotrovimab be funded for the treatment of COVID-19 for high-risk immunocompromised patients, as a strategic contingency for possible future sotrovimab-susceptible SARS-CoV2 variants, subject to the following Access Criteria:

Initial Application – (treatment of COVID-19 for high-risk immunocompromised patients)

Any relevant practitioner. Approvals valid for 1 week for all applications meeting the following criteria:

All of the following:

1. Patient is immunocompromised* AND not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection, regardless of vaccination status; or confirmed deficiency of a (neutralising) serological response; and
2. Patient has confirmed (or probable) symptomatic COVID-19 or has symptoms consistent with COVID-19 and is a household contact of a positive case; and
3. COVID-19 is confirmed or very likely due to a sotrovimab-susceptible SARS-CoV-2 variant; and
4. Patient's symptoms started within the last 5 days; and
5. Any of:
    - 5.1. Patient does not require supplemental oxygen (oxygen saturation >93%); or
    - 5.2. Patient does not require supplemental oxygen to maintain oxygen saturations at or above baseline (for patients with chronic resting hypoxia).

Notes:.

* As per Ministry of Health criteria(external link) of 'severe immunocompromise' for third primary dose

2.2. In making these recommendations, the Advisory Group considered the high health need for patients with COVID-19 who are immunocompromised and at high risk of developing severe disease.

2.3. The Advisory Group noted that an application for sotrovimab has not yet been submitted to Medsafe for consideration.

2.4. The Advisory Group noted that sotrovimab has been authorised for use in overseas jurisdictions including Australia, Canada, Singapore, and the EU. The Advisory Group also noted that on April 5th, 2022, the US FDA reversed its emergency use authorisation for sotrovimab due to concerns that it is unlikely to be effective against the BA.2 subvariant of Omicron.

2.5. The Advisory Group noted that no priority ranking (within the context of treatments for COVID-19) was sought by Pharmac, reflecting the rapidly evolving evidence for treatments in COVID-19 and separate funding outside the Combined Pharmaceutical Budget, and therefore did not need to discuss a priority ranking.

2.6. The Advisory Group reiterated this was an area of rapidly evolving evidence and knowledge and specified that its recommendation may need to be considered in the future, noting this was based on currently available data from published studies and could be subject to change should new data become available, warranting further review.

3. Discussion

3.1. The Advisory Group noted that there are seven pharmaceuticals funded explicitly for the treatment of COVID-19 in New Zealand, including tocilizumab, remdesivir, baricitinib, nirmatrelvir plus ritonavir, casirivimab plus imdevimab, molnupiravir (subject to Medsafe approval), and tixagevimab plus cilgavimab (subject to Medsafe approval).

3.2. The Advisory Group noted that sotrovimab is a monoclonal antibody that binds to a highly conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 but does not compete with human angiotensin converting enzyme 2 (ACE2) receptor binding. The Advisory Group noted that sotrovimab includes two amino acid substitutions to the Fc domain that extend the half-life of the antibody, which may improve bioavailability in the respiratory mucosa.

3.3. The Advisory Group noted that sotrovimab is administered as a single 500 mg dose administered as an intravenous infusion over 30 minutes for adults and paediatric patients aged ≥12 years and weighing ≥40 kg. The Advisory Group noted that sotrovimab should be administered as soon as possible after a positive test result and within 5 days of the onset of symptoms.

3.4. The Advisory Group considered that the primary clinical evidence supporting the use of sotrovimab for the treatment of COVID-19 is provided by the ongoing, multicentre, double-blind, phase 3 COMET-ICE trial (Gupta A, et al. N Engl J Med. 2021;385:1941- 50; Gupta A, et al. JAMA. 2022;327:1236-46).

3.4.1. Eligible patients were ≥18 years of age, had symptomatic COVID-19 (≤5 days of symptom onset), were non-hospitalised, and had at least one risk factor for disease progression: older age (>55 years), diabetes for which medication was warranted, obesity (body mass index [BMI] >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate-to-severe asthma.

3.4.2. The Advisory Group considered that, given the timeframe of the trial (all patients were allocated to treatment by 11 March 2021), the patients were unlikely to be vaccinated against Sars-CoV-2 and would not have been infected with the Omicron Variant of COVID-19.

3.4.3. The Advisory Group noted that patients who were considered severely immunocompromised (eg. cancer patients receiving immunosuppressive

chemotherapy or immunotherapy, patients who had undergone a solid organ transplant or allogeneic stem cell transplant within 3 months, or those requiring systemic corticosteroids) were excluded from the COMET-ICE trial.

3.4.4. The Advisory Group noted that patients were randomly assigned (1:1) to receive either a single 500 mg, 1-hour infusion of sotrovimab or an equal volume of saline placebo on day 1.

3.4.5. The primary outcome was the percentage of patients hospitalised for more than 24 hours or who died from any cause through day 29 after randomisation. Secondary outcomes included the percentage of patients with an emergency department visit, hospitalisation, or death, and the percentage of patients who had disease progression that warranted supplemental oxygen.

3.4.6. The Advisory Group noted that the duration of symptoms was ≤3 days for 58% of patients.

3.4.7. At the time of the prespecified interim analysis (Gupta A, et al. N Engl J Med. 2021;385:1941-50), 1% (3/291) of patients in the sotrovimab arm and 7% (21/292) in the placebo arm had disease progression leading to hospitalisation (>24 hours) or death (relative risk reduction, 85% [97.24% CI, 44-96]; *P* = 0.002). Adverse events were reported by 17% (73/430) and 19% (85/438) of patients, respectively.

3.4.8. The Advisory Group noted that several items of correspondence were published in the journal in response to the prespecified interim analysis of COMET-ICE (Correspondence. Early Treatment with Sotrovimab for COVID-19. N Engl J Med. 2022;386:1480-1). The Advisory Group considered the primary issues raised were that the population did not truly reflect a high-risk population and that severely immunocompromised patients were excluded.

3.4.9. At the time of the primary analysis (Gupta A, et al. JAMA. 2022;327:1236-46), 1% (6/528) patients in the sotrovimab arm and 6% (30/529) in the placebo arm had disease progression leading to hospitalisation (>24 hours) or death (relative risk reduction, 79% [95% CI, 0.09-0.50]; *P* <0.001). The Advisory Group noted that four of five secondary outcomes were also considered to be statistically significant in favour of sotrovimab. Adverse events were reported by 22% (114/523) of patients in the sotrovimab arm and 23% (123/526) in the placebo arm.

3.5. The Advisory Group considered clinical data provided by a real-world, observational, cross-sectional study conducted in patients hospitalised for COVID-19 in Singapore in October 2021 (Ong SWX, et al. Antibiotics [Basel]. 2022;11:345). The Advisory Group noted that of 94 patients analysed, only 19 (20.2%) received sotrovimab. The results suggested patients who received sotrovimab had a lower progression to oxygen requirement (31.6% vs 54.7%), ICU admission (10.5% vs 24.0%), or mortality (5.3% vs 13.3%) than patients who did not receive pre-emptive treatment, and had slower time to in-hospital deterioration (HR, 0.41 [95% CI, 0.17-0.99]; *P* = 0.047).

3.6. The Advisory Group considered the results of a preclinical study of the antiviral activity of the monoclonal antibodies, sotrovimab and VIR-7832 (Case JB et al. bioRxiv preprint; March 18, 2022). The results showed that sotrovimab effectively neutralised SARS-CoV-2 in a live virus assay as well as in pseudotyped virus variants of concern. The Advisory Group considered that in addition to its neutralising capacity, sotrovimab was shown to mediate antibody dependent cellular cytotoxicity and antibody dependent cellular phagocytosis.

3.7. The Advisory Group considered the results of two *in vitro* studies which examined the neutralising ability of approved and investigational monoclonal antibodies against SARS-CoV-2 variants of concern.

3.7.1. The earlier study (Takashita E, et al. N Engl J Med. 2022;386:995-8) showed that S309, the precursor of sotrovimab, neutralised earlier strains of SARS-CoV-2 (NC002, alpha, and delta) with a low $FRNT_{50}$ (50% focus reduction neutralisation test) value, and retained neutralising activity against beta, gamma, and omicron (B.1.1.529), albeit with higher $FRNT_{50}$ value for Omicron.

3.7.2. The more recent study (Takashita E, et al. N Engl J Med. 2022;386:1475-7) assessed the neutralising ability of monoclonal antibodies against the BA.2 subvariant of omicron. The results showed that S309, the precursor of sotrovimab, had lower neutralising activity against omicron/BA.2 than it did against the ancestral strain or other variants of concern including omicron/BA.1.1. Omicron variants (BA.1, BA.2) were generally substantially less neutralised by available monoclonal antibody therapies, than were earlier variants. The reason for this is uncertain but could reflect SARS-CoV2 evolving in response to vaccination.

3.8. The Advisory Group noted ESR national whole genome sequencing (WGS) reports as that of April 13th, the BA.2 subvariant of Omicron accounted for 97% of all sequenced cases of COVID-19 in New Zealand, and 77% of all hospitalised cases.

3.9. The Advisory Group considered that the efficacy of sotrovimab may be limited in the BA.2 subvariant of omicron, but that it could have efficacy in other future emergent variants of SARS-CoV-2. The Advisory Group considered that having to identify variants susceptible to sotrovimab before treatment using WGS or other methods within a rapid turn-around time would require significant laboratory capacity.

3.10. The Advisory Group considered the evolving landscape of COVID-19, and how this has impacted outcomes of interest in New Zealand. The Advisory Group considered that the apparent national focus has considerably shifted from preventing infection and transmission to reducing progression to severe disease, hospitalisation, and mortality. The Advisory Group considered that while long-term morbidity is of interest, limited data are available at this time.

3.11. The Advisory Group considered that risk factors for hospitalisation with the omicron variant of SARS-CoV-2 in New Zealand include lack of vaccination, older age, and comorbidities. The Advisory Group also considered that Māori and Pacific populations are at higher risk for developing severe COVID-19, which may reflect factors including unrecognised comorbidity burden.

3.12. The Advisory Group considered the high health need of patients who are profoundly immunocompromised due to conditions such as solid organ transplant, cancer, or primary immunodeficiencies (e.g. common variable immunodeficiency [CVID] and rheumatological disorders), or because of treatment with immunomodulators, immunosuppressive chemotherapy, or immunotherapy. The Advisory Group considered that monoclonal antibodies against SARS-CoV-2, such as sotrovimab, may have a role in decreasing the risk of progression to severe disease in immunocompromised patients or in treating persistent infection or severe illness.

3.13. The Advisory Group noted that some profoundly immunocompromised patients experiencing severe or persistent COVID-19 are currently being treated with convalescent plasma. The Advisory Group considered there are limited data supporting its use in COVID-19.

3.14. The Advisory Group considered that monoclonal antibodies may be of value for patients at high risk of drug-drug interactions, for whom antivirals can be contraindicated.

3.15. The Advisory Group noted that the requirement for sotrovimab to be administered as an intravenous infusion would present a barrier to access. The Advisory Group also noted that preliminary results of the phase 3 COMET-TAIL study suggest that intramuscular sotrovimab is non-inferior to intravenous sotrovimab. The Advisory Group noted that no peer-reviewed data for COMET-TAIL are yet available.

3.16. The Advisory Group considered a retrospective analysis of 8 patients with RT-PCR assays that were persistently positive for SARS-CoV-2 for whom respiratory tract specimens were available from before and after treatment with sotrovimab (Rockett R, et al. N Engl J Med. 2022;386:1477-9). The study reported that 4 (50%) of these patients acquired previously defined receptor-binding domain mutations within 6-13 days of receiving sotrovimab, and that cultures from these patients remained positive for 23, 24, 12, and 15 days, respectively. The Advisory Group considered that these data suggest resistance mutations may be a concern for monoclonal antibody treatments for COVID-19.

3.17. The Advisory Group considered that the strength and quality of the evidence for sotrovimab was moderate when considered for an unvaccinated population infected with earlier SARS-CoV-2 variants. The Advisory Group considered the strength and quality of evidence was low when these data are extrapolated to the current population in New Zealand, which is largely vaccinated and dominated by the BA.2 subvariant of omicron.

3.18. The Advisory Group considered there was potential for sotrovimab to be used in combination with antiviral agents in profoundly immunocompromised patients, if infected with a susceptible variant.

3.19. The Advisory Group noted literature evidence related to the serological responses of profoundly immunosuppressed people to SARS-CoV2 vaccination courses, and the limitations of neutralising antibody responses as surrogate markers of protection against serious outcomes.

3.20. The Advisory Group considered that the below PICO (population, intervention, comparator, outcomes) reflects the population that would benefit most from sotrovimab, if it were to be funded in New Zealand.

Table 1: PICO for sotrovimab if it were to be funded in New Zealand for high-risk immunocompromised patients COVID-19.

Population	High-risk immunocompromised patients with COVID-19
Intervention	Sotrovimab 500 mg IV
Comparator(s) (NZ context)	Standard of care Molnupiravir Nirmatrelvir with ritonavir Tixagevimab with cilgavimab*
Outcome(s)	Prevention of progression to severe COVID-19 Possible reduction in hospitalisations Prevention of COVID-19 mortality
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)	

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

*Tixagevimab with cilgavimab was not available in New Zealand at the time of the Advisory Groups April 2022 meeting.

3.21. The Advisory Group considered that there is uncertainty regarding the number of high-risk immunocompromised patients in New Zealand, partly as it is a heterogeneous group and the specific at-risk group are yet to be defined. It is also uncertain how many of this group will acquire COVID-19 following preventative measures, and the future proportions of SARS-CoV2 variants in NZ.

Review of evidence for tixagevimab with cilgavimab against the Omicron variant and other emerging variants of COVID-19

1. Application

The Advisory Group considered evidence regarding the use of tixagevimab with cilgavimab in the treatment of the Omicron variant and other emerging subvariants of COVID-19

2. Recommendations

1.1. The Advisory Group recommended that tixagevimab and cilgavimab be funded for the prophylactic treatment of COVID-19, subject to the following criteria.

Access criteria
Indication – Prophylaxis of COVID-19
Any relevant practitioner.
Approvals valid for 1 week for all applications meeting the following criteria:
All of the following:

1. Either
    a. Patient is at risk of inadequate immune response to SARS-CoV-2 vaccination or infection due to severe immunocompromise; and
    b. Patient has returned a SARS-CoV-2 antibody assay indicating inadequate immune response to SARS-CoV-2 vaccination or infection; or
    c. Patient has received a lung transplant; or
    d. Patient is not able to be vaccinated against COVID-19 for a medical reason.
2. Patient does not currently have SARS-CoV-2 infection

3. Discussion

1.2. The Advisory Group noted that that at the time of its previous 13 December 2021 meeting the Delta variant of COVID-19 was dominant in New Zealand, with small numbers of cases of the Omicron variant beginning to emerge.

1.3. The Group considered that as the Omicron variant of COVID-19 and its subvariants were now (in April 2022) the dominant variants of COVID-19 both in New Zealand and globally, it was timely to consider the available evidence for the effectiveness of tixagevimab with cilgavimab against the Omicron variant of COVID-19.

1.4. The Advisory Group considered available clinical evidence for tixagevimab with cilgavimab for the treatment of people with COVID-19:

1.4.1. The Advisory Group noted that a study Loo YM et al. Sci Transl Med. 2022 had recently been published. The authors reported that that tixagevimab with

cilgavimab was protective in non-human primates against COVID-19 infection and had an extended half-life in humans.

1.4.1.1. The Advisory Group noted that tixagevimab with cilgavimab neutralized the USA-WA1/2020 reference strain of SARS-CoV-2 (IC50 10 ng/ml) and retained neutralising activity (fold-change IC50 <3.0) against SARS-CoV-2 Alpha, Beta, Gamma, and Delta Variants compared USA-WA/1/2020 or AUS/IC01/2020.

1.4.1.2. The Group noted that in non-human primates treated prophylactically with 4 mg/kg (comparable to the human 300 mg dose) of tixagevimab with cilgavimab, SARS-CoV-2 viral subgenomic messenger RNA (sgmRNA) was undetectable in bronchoalveolar lavage (BAL) up to 14 days post infection, which may suggest that prophylactic treatment with tixagevimab with cilgavimab may protect against lower respiratory tract infection. low concentrations of sgmRNA were detected transiently (day 2 only) in nasal swab samples.

1.4.1.3. The Advisory Group noted that in the treatment of COVID-19 tixagevimab with cilgavimab was much less effective at reducing virus titres in BAL samples and nasal swab samples; however, accelerated viral clearance was observed in non-human primates treated with tixagevimab with cilgavimab compared to isotope control.

1.4.1.4. The Group noted that the non-human primates were challenged with the USA-WA1/2020 reference strain of SARS-CoV-2 and therefore the outcomes observed may not necessarily apply to other variants of COVID-19.

1.4.1.5. The Advisory group noted that the authors had also compared the ratio of neutralising antibodies in serum following a single IM dose of 300 mg AZD7442 to neutralising antibodies in convalescent serum samples in humans. This showed that, within one week following administration, tixagevimab with cilgavimab neutralising antibody concentrations were approximately 25-fold greater than those associated with convalescent serum. These concentrations remained 3-fold higher for 9 months.

1.4.2. The Advisory Group noted that the manufacturer of tixagevimab with cilgavimab (AstraZeneca) was undertaking a number of trials, to assess the effectiveness of tixagevimab with cilgavimab in the treatment of COVID-19, which were ongoing and results had not been published.

1.4.3. The Advisory Group noted that Mahase E. BMJ. 2021;375 provided a summary of the results that had been reported to date in the Phase III PROVENT and TACKLE trials.

1.4.3.1. Prophylactic treatment against COVID-19 – PROVENT
One 300 mg dose of tixagevimab with cilgavimab reduced the risk of developing symptomatic COVID-19 by 83%, when compared with placebo in unvaccinated people who did not have signs of previous SARS-CoV-2 infection.

1.4.3.1.1. The Advisory Group noted the low number of events in the trial, with 5,197 people enrolled and 25 cases of COVID-19 reported.

1.4.3.2. Treatment of COVID-19 – TACKLE

One 600 mg dose of tixagevimab with cilgavimab reduced the risk of developing severe COVID-19 or death (from any cause) by 88% compared with placebo in non-hospitalised adults with mild to moderate COVID-19 in patients who had been symptomatic for three days or less at the time of treatment.

1.4.3.2.1. The Advisory Group noted that the 88% reduction reflected a subgroup of patients treated within three days of symptom onset.

1.4.4. The Advisory Group noted a preprint of a study Benotmane, et al. bioRxiv 2022 which raised concerns about breakthrough cases of the Omicron BA.1, BA.1.1 and BA.2 variants of COVID-19 in kidney transplant patients and received tixagevimab with cilgavimab prophylactically. The Advisory Group noted that of the 416 kidney transplant patients who received prophylactic injections of tixagevimab with cilgavimab, 39 (9.4%) developed COVID-19. SARS-CoV-2 sequencing was carried out in 15 of the which found that only one of the cases was the BA.2 subvariant. The other cases were the BA.1 subvariant (n=5) and the BA1.1 subvariant (n=9).

1.4.5. The Advisory Group noted a preprint of a study Bruel, et al. Nat Med, 2022 which evaluated serum neutralisation of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. The authors found that cilgavimab retained an IC50 of 9.3 ng/ml and the addition of tixagevimab to cilgavimab did not offer additional neutralisation benefits. The authors also measured antibody levels and neutralisation activity in the sera of 29 immunocompromised individuals before and after administration of tixagevimab with cilgavimab and reported that neutralisation of BA.1 and BA.2 Omicron subvariants was detected in 19 out of 29 and 29 out of 29 tixagevimab with cilgavimab recipients, respectively.

1.4.6. Advisory Group noted a preprint of a study Case, et al. bioRxiv 2022 which evaluated the effectiveness of sotrovimab and tixagevimab with cilgavimab against the Omicron variant of COVID-19 and its subvariants in human Fcγ R transgenic mice. The Advisory Group noted that sotrovimab largely retained neutralisation activity against the BA.1 and BA.1.1 variants of COVID19 (EC50, 452.0 and 7.7.4 compared to 185.2 for the reference strain of SARS-CoV-2), however, sotrovimab showed a significant decrease in the neutralisation capacity against the BA.2 variant of COVID-19 (EC50 5,885). In contrast tixagevimab with cilgavimab showed retained neutralisation activity against the BA.1 and BA.2 variants of COVID-19 (EC50, 166.6 and 35.4 respectively) compared to 6.5 for the reference strain of SARS-CoV-2. Tixagevimab with cilgavimab demonstrated significantly reduced neutralisation capacity against the BA.1.1 variant of COVID-19 (EC50 1,146.8).

1.4.6.1. The Advisory Group noted that the study was yet to be published and therefore any results reported were indicative only. In addition, the Advisory Group noted that the study had been undertaken in transgenic mice and may not apply directly to humans.

1.4.7. The Advisory Group noted treatment with tixagevimab with cilgavimab did not significantly reduce BA.1.1 lung viral RNA in transgenic mice however, the presence of BA.2 lung viral RNA was significantly reduced following treatment with tixagevimab with cilgavimab. The Group noted that as with the results reported by Loo YM et al. Sci Transl Med. 2022 in non-human primates, the

presence of SARS-CoV-2 viral RNA in the nasal turbinates and nasal wash in transgenic mice was not significantly reduced following treatment with tixagevimab with cilgavimab. The Advisory Group considered that may reflect reflected emerging evidence that nasopharyngeal viral load is not necessarily a reliable indicator of lung injury from COVID-19 infection.

1.4.8. The Advisory Group noted heat maps which demonstrated a reduction in cytokine and chemokine generation in the lung tissue of transgenic mice infected with COVID-19 following treatment with tixagevimab with cilgavimab. The Group considered that this demonstrated that treatment of the BA.2 variant of COVID-19 with tixagevimab with cilgavimab resulted in a reduction in lung viral RNA and the inflammatory response to COVID-19, which typically results in lung injury.

1.4.9. The Advisory Group considered that the available evidence indicates that in vitro studies show that neutralisation titres when using tixagevimab with cilgavimab against Omicron subvariants are higher than those against the reference strains of COVID-19 and performs better against BA.2 compared to the BA.1 and BA.1.1 subvariants. Results of in vivo studies reported by Case, et al. bioRxiv 2022 demonstrate that pre-treatment with tixagevimab with cilgavimab may reduce concentrations of viral RNA in the lungs compared to isotype control and reduces cytokine and chemokine generation in the lung.

1.4.10. The Advisory Group noted that data regarding the safety profile for tixagevimab with cilgavimab in the prevention and treatment of COVID-19 was continuing to emerge and would be reviewed by the Advisory Group as new evidence becomes available.

1.5. The Advisory Group noted the recent recommendation from the FDA that a double dose of tixagevimab with cilgavimab is required to achieve protection against the Omicron variant of COVID-19. The Advisory Group noted that at the time that this recommendation was made the BA.1 and BA.1.1 subvariants were the dominant variants of COVID-19. Based on the available evidence the Advisory Group noted the studies by Bruel, et al. Nat Med, 2022 and Case, et al. bioRxiv 2022 and considered that that an increased dose of tixagevimab with cilgavimab would not be required to achieve neutralisation of the BA.2 Omicron subvariant of COVID-19, which was dominant in New Zealand. The Advisory Group considered it would be important to continue to monitor the effectiveness of COVID-19 against emerging variants of COVID-19 and consider dose adjustments as required.

1.6. The Advisory Group noted information released by the supplier that 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.

1.7. The Advisory Group noted that at its 13 December 2021 meeting it had previously recommended that tixagevimab with cilgavimab be funded for the treatment of people with COVID-19; however, the Advisory Group noted that to date AstraZeneca has not sought regulatory approval of tixagevimab with cilgavimab for this indication internationally and does not have immediate plans to submit a dossier for this use in New Zealand. Funding of tixagevimab with cilgavimab for use in the treatment of people with COVID-19 infection may be considered at a later date.

1.8. The Advisory Group considered the target population for tixagevimab with cilgavimab and noted that people with immunodeficiencies have considerably worse

outcomes from COVID-19 infection and are at greater risk of hospitalisation or mortality from COVID-19 infection than the general population. The Advisory Group noted that it was expected that approximately 60% of these patients would mount an immune response to COVID-19 vaccination, however at significantly lower titres than the general population.

1.9. The Advisory Group considered that available evidence suggests that tixagevimab with cilgavimab would offer the greatest benefit to high needs patients with primary and secondary immunodeficiency particularly if they are infected with the Omicron BA.2 subvariant.

1.10. The Advisory Group considered that approximately 60% of solid organ transplant patients mounted an immune response following COVID-19 vaccination and this was further improved following additional doses. The Advisory Group noted there was conflicting data regarding severity of outcomes in solid organ transplant patients infected with COVID-19 as this appears to be affected by the organ being transplanted, with lung transplant patients receiving particularly poor outcomes compared to liver and kidney transplant patients, which tend to have better outcomes.

1.11. A Member noted emerging data from the Auckland region which suggested that doses of one gram or more of mycophenolate appeared to be the predominant risk factor for poor vaccine responsiveness in renal transplant patients.

1.12. The Advisory Group noted that the Ministry of Health's eligibility criteria for a third primary dose of COVID-19 vaccine could be used to determine access to tixagevimab with cilgavimab . Noting the limited volume of stock that had been secured (20,000 treatment courses), the Advisory Group considered that the Ministry of Health's eligibility criteria included a number of patient populations that were not at significantly increased risk of severe COVID-19 or hospitalisation. In particular, the Group noted that the criteria included patients on immunosuppressive therapies and biologics and people on peritoneal dialysis or haemodialysis. The Advisory Group considered the majority of these patients would not require access to tixagevimab with cilgavimab.

1.13. The Advisory Group noted the Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19 published by the British Columbia COVID Therapeutics Committee, based on a clinical appraisal of available Omicron BA.2 data. The Group noted that this guide establishes three levels of clinically extremely vulnerable people to prioritise COVID-19 Treatments. The Advisory Group noted that the most severe group (CEV1 included severe immunocompromise, treatment for haematological malignancy and those receiving anti-CD20 or B-cell depleting therapies.

1.14. The Advisory Group considered that the majority of patients on immunosuppressive therapies and biologic treatments and people on peritoneal dialysis or haemodialysis would not require access to tixagevimab with cilgavimab for protection or treatment against COVID-19 vaccination.

1.15. The Advisory Group considered it would be reasonable for tixagevimab with cilgavimab be available for lung transplant patients but did not consider that access for other solid organ transplant recipients would be required explicitly in the access criteria.

1.16. The Advisory Group considered that the access criteria should also provide access for the small number of patients unable to be vaccinated for medical reasons.

1.17. The Advisory Group 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.

1.18. The Advisory Group noted that Pharmac's Exceptional Circumstances Framework would remain available for individuals with exceptional circumstances that did not meet the access criteria.

1.19. The Advisory Group considered that to target tixagevimab with cilgavimab to people with the greatest health need, antibody blood concentration testing should be included in the access criteria to indicate clinical need. The Advisory Group noted that there are a number of tests available that could be used for this purpose ranging from relatively simple spike protein antibody assays that could be used to identify whether or not a person has mounted an immune response to COVID-19 vaccination or infection, or more comprehensive laboratory tests such as the cPass test which may offer greater specificity regarding the level of neutralisation achieved. The Advisory Group noted a Research Letter Fox-Lewis ,et al 2020 NZMJ comparing SARS-CoV-2 antibody assays in Auckland, New Zealand.

1.20. The Advisory Group noted that compared to other ethnic groups Māori and Pacific peoples were disproportionately represented in COVID-19 statistics in New Zealand including in terms of case numbers and, hospitalisations and considered it would be important for tixagevimab with cilgavimab to be available to Māori and Pacific peoples who meet the access criteria.

1.21. The Advisory Group noted equity concerns regarding access to antibody testing throughout New Zealand, particularly if more comprehensive laboratory tests such as the cPass test were to be used. The Advisory Group considered this would be a particular concern for rural or remote populations without access to large DHB Hospitals, with Māori highly affected in this setting.

The Advisory Group considered it would be useful for the use and availability of antibody testing to be discussed further with the Ministry of Health's COVID-19 Testing Technical Advisory Group, to gain a better understanding of this.

Oral antivirals (nirmatrelvir with ritonavir; molnupiravir) access criteria

1. Discussion

1.2. The Group discussed the access criteria for oral antiviral treatments based on concerns raised to Pharmac that recently-funded uptake of nirmatrelvir with ritonavir had been lower than expected.

1.3. The Group noted significant concerns with the low number of prescriptions and considered that, based on available information, nirmatrelvir with ritonavir is one of the most effective treatments available for COVID-19 in New Zealand and therefore it is important that it is used to treat people at risk of severe COVID-19.

1.4. The Group considered that the low prescribing rate for nirmatrelvir with ritonavir may in part be due to the nature of their access criteria, however, the Group considered

there are likely to be a number of additional contributing factors, including the novelty of the treatment and the speed with which it has been implemented in New Zealand, combined with the ongoing burden on the health sector due to the COVID-19 pandemic and the drug/drug interactions associated with ritonavir and a large number of commonly prescribed medicines.

1.5. The Group considered that these factors may be creating hesitancy amongst clinicians to prescribe nirmatrelvir with ritonavir. Consequently, the Group considered that even if the access criteria were widened to include a larger patient population, it may not result in a significant increase in uptake.

1.6. The Group considered it was important to promote the responsible prescribing of COVID-19 treatments to encourage use of these treatments amongst people most likely to benefit. The Group considered that it would be important to ensure that the access criteria were practical and simple to interpret and implement and that clinical guidance information was available to support decision making.

1.7. In addition to low prescribing rates, the Group noted feedback received by Pharmac that some conditions which may increase a person's risk of severe COVID-19 were not appropriately reflected in the access criteria. The Group noted specific feedback that people with Down Syndrome are at increased risk of severe COVID-19 and that a submitter had consequently requested that Down Syndrome should be included explicitly as a health condition for access to oral antiviral treatments for COVID-19.

1.8. The Group considered a prospective cohort study of vaccinated individuals (Hippisley-Cox et al. BMJ. 2021;374:n2244) undertaken in the United Kingdom which noted that individuals with Down Syndrome had a 12.7 fold increased risk of mortality due to COVID-19. The study also noted that people with sickle cell disease had a 7.7 fold increased risk of mortality from COVID-19.

1.8.1. The Group noted that this study also identified other patient groups that may be at increased risk of mortality from COVID-19, such as care home residency, chemotherapy and recent bone marrow transplantation. The Group considered however that these groups would be covered by the existing access criteria.

1.9. Members noted that there is emerging evidence that learning disabilities are associated with increased risk of mortality or hospitalisation resulting from COVID-19 for all people with intellectual disabilities. The Group however considered that, compared to other groups with intellectual disabilities, increased risk of severe COVID-19 appeared to be a particular risk for people with Down Syndrome, which may be a result of the cardiac abnormalities and immune dysregulation associated with the condition.

1.10. Noting the above evidence, the Group considered it would be reasonable to amend criterion 3.1 of the oral antiviral treatments access criteria to include Down Syndrome and sickle cell disease as explicit conditions for access to oral antiviral COVID-19 treatments, and was supportive of other intellectual disabilities being recognised risk factors for severe disease.

1.11. The Group considered information published by the British Columbia COVID-19 Therapeutics Committee which illustrated the risk of hospitalisation as a result of COVID-19 for various populations which are not considered to be clinically extremely vulnerable (i.e. patients not in Clinically Extremely Vulnerable Groups 1-3). The Group noted that people who had not received any doses of vaccination

against COVID-19, with three or more risk conditions, and people aged 70 years and over who had received fewer than three doses of COVID-19 vaccination were at the highest risk of hospitalisation in the subset of patients not classed as clinically extremely vulnerable.

1.12. Members noted that the Ministry of Health's COVID-19 Therapeutics Advisory Group (TAG) was preparing a submission regarding the access criteria for antiviral treatments, as members of the TAG considered that vaccination status as a risk factor for severe COVID-19 is not appropriately reflected in the current oral antiviral treatments' access criteria.

1.13. The Group noted this feedback would be considered in detail once it has been received.

1.14. Considering the information published by the British Columbia COVID-19 Therapeutics Committee and the low uptake rate of nirmatrelvir with ritonavir prescriptions, the Advisory Group was supportive of amending if required the count of factors for access to oral antiviral treatments and the age of access, to ease access for at risk people.

1.15. The Group noted that, in addition to nirmatrelvir with ritonavir, Pharmac had also secured supply of molnupiravir, another oral antiviral treatment for COVID-19. The Group noted that molnupiravir was not approved by Medsafe and was undergoing Medsafe assessment. The Group noted that, if approved, molnupiravir could be available in New Zealand from late April 2022.

1.16. The Group was supportive of the access criteria for antiviral treatments (including nirmatrelvir with ritonavir, molnupiravir and remdesivir) being aligned as much as possible, noting however that differences may be necessary to reflect factors such as availability and efficacy.

1.17. The Group noted that compared to nirmatrelvir with ritonavir, molnupiravir is expected to be simpler to prescribe as it does not have the same drug/drug interactions. The Group raised concerns that this could lead to molnupiravir being prescribed by clinicians in favour of nirmatrelvir with ritonavir, even although available data published by Bernal et al 2022 and Hammond et al 2022 indicates that nirmatrelvir with ritonavir reduces the risk of COVID-19 related hospitalisation or death compared to placebo by ~89%, compared with ~30% for molnupiravir.

1.18. The Group considered that, on the basis of efficacy, it would be appropriate to amend the access criteria to reflect that nirmatrelvir with ritonavir is the preferred oral antiviral treatment for COVID-19.