Record of the COVID-19 Therapeutics Advisory Group Meeting held via video conference on 21 October 2021

Note that this document is not necessarily a complete record of the COVID-19 Therapeutics Advisory Group meeting held on 21 October 2021; rather it is a summary of the pertinent discussion at the meeting

Present from the COVID-19 Therapeutics Advisory Group

Jane Thomas
Brian Anderson
Kerry Benson-Cooper
Tim Cutfield
Eamon Duffy
Jessica Keepa
Graham Mills
Stephen Munn
Marius Rademaker
Nigel Raymond
Justin Travers

Observers
Dan Bernal
Anne Buckley

Summary of recommendations

1.1. The following recommendation summary is an order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
• Molnupiravir for the treatment of mild to moderate symptomatic COVID-19.	Recommended
• Casirivimab and imdevimab in hospital for the treatment of mild to moderate- symptomatic COVID-19.	Recommended
• Casirivimab and imdevimab in the community for the treatment of profoundly immunocompromised people with symptomatic COVID-19.	Recommended
• Casirivimab and imdevimab for patients in the community with asymptomatic COVID-19, or mild symptomatic COVID-19..	Not recommended
• Casirivimab and imdevimab for the treatment of close contacts of positive cases with COVID-19.	Not recommended
• Baricitinib for the treatment of moderate-severe COVID-19.	Recommended

Molnupiravir for the treatment of COVID-19

1. Application

1.1. The Advisory Group reviewed material provided by the Supplier and Pharmac staff regarding the use of molnupiravir for the treatment of COVID-19.

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

2. Recommendation

2.1. The Advisory Group **recommended** molnupiravir be funded, subject to Medsafe approval, for the treatment of mild to moderate COVID-19, subject to the following Special Authority / Hospital Restriction criteria.

Initial Application – (treatment of mild to moderate COVID-19) Any relevant practitioner. Approvals valid for 1 week for all applications meeting the following criteria:

All of the following:

1. Patient has confirmed (or probable) symptomatic COVID-19; and
2. Patient is ≤5 days of symptom onset; and
3. Patient does not require supplemental oxygen (oxygen saturation >93%).
4. Either:
    a. Age > 60years; or
    b. BMI $\geq$ 30; or

c. Patient is at risk of severe illness from COVID-19, excluding pregnancy, as described on the Ministry of Health website

2.2. In making this recommendation, the Advisory Group considered the high health need and limited treatment options for patients with mild to moderate COVID-19, the equity implications of COVID-19, likelihood of a higher mortality rate for patients with comorbidities and the impact to the health system particularly the potential for a reduction in hospital admissions.

2.3. Members noted molnupiravir is not currently approved for use in New Zealand and is expected to be submitted to Medsafe for review in mid-January 2022.

2.4. The 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.

2.5. 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 and unpublished studies and could be subject to change should new data become available, warranting further review.

3. Discussion

3.1. The Group noted that there are two pharmaceuticals explicitly funded for treatment of COVID-19 in Aotearoa New Zealand, tocilizumab and remdesivir and that both are funded for treatment of moderate-severe COVID-19 in hospitalised patients. The Group considered that there is an unmet health need for treatment of symptomatic mild-moderate COVID-19 and prophylaxis of COVID-19.

3.2. The Group considered that the rate of hospitalisations in New Zealand was approximately 9% of all cases and that patients >40 years had the highest rate of hospitalisations based on age alone. However, Members considered that ongoing vaccination is expected to reduce the hospitalisation rate in the future by reducing both the number and severity of cases, and therefore the rate of hospitalisations (9%) is only valid at this point and time (21 October 2021).

3.3. The Group noted that the health need of those with COVID-19 is high for the individual, their whanau, the wider community.

3.4. The Group considered the impact of COVID-19 to the health system. Members considered that treatments that significantly reduce the risk of hospitalisation and severity of illness would be of great benefit.

3.5. The Group noted molnupiravir is an antiviral prodrug of ribonucleoside N4-hydroxycytidine (NHC) which forms NHC-Triphosphate (NHC-TP). The mechanism of action of molnupiravir as an antiviral drug is via acting as a competitive alternative substrate for the RNA dependent RNA polymerase (RdRp) enzyme in the SARS-CoV2 virus, resulting in viral error catastrophe and production of non-viable virus.

3.5.1. The Group considered that the mechanism of action is such (false metabolite interfering with the RNA-dependent RNA polymerase) that it is likely to be independent of COVID-19 mutations, either current or emerging.

3.5.2. The Group considered that the five day treatment course made the likelihood of the emergence of treatment resistant variants less likely, as this is an acute infection unlike for example hepatitis C virus-related chronic infection.

3.6. The Advisory Group considered clinical evidence regarding molnupiravir for treatment of mild-moderate COVID-19, specifically the following:

3.6.1. MOVe-IN Phase 2/3 trial; Unpublished data
A phase 2/3 randomised, placebo controlled, double-blind trial in 304 adults requiring in-hospital treatment for COVID-19 with symptom onset less than 10 days. The trial evaluated molnupiravir 200mg, 400mg and 800mg vs placebo and did not report a clinical benefit in hospitalised patients.

3.6.2. MOVe-OUT Phase 2 trial; Unpublished data
A phase 2 randomised, placebo controlled, double-blind trial in 302 non-hospitalised patients with COVID-19, who were symptomatic for less than 7 days. The trial evaluated molnupiravir 200mg, 400mg and 800mg vs placebo and the authors reported a reduced number of patients progressing to hospitalisation with greater effects for doses of molnupiravir given <5 days after symptom onset.

3.6.3. MOVe-OUT Phase 3 trial; Unpublished data
A phase 3 randomised, placebo controlled, double-blind trial in 775 non-hospitalised patients with mild-moderate COVID-19 confirmed via laboratory testing less than 5 days prior to randomisation.
All patients were in defined at risk groups (age 60+, 1 or more co-morbidities including obesity, diabetes, heart disease).
An interim analysis showed molnupiravir significantly reduced the risk of hospitalisation and death by approximately 50%; 7.3% vs 14.1% placebo; p=0.0012.
Based on the interim analysis hospitalisations in adults 60 years and older were reported to be 6 times higher in the placebo group than the molnupiravir treated group (3.6% vs 21.4%).
The incidence of adverse events was comparable in the molnupiravir and placebo groups (35% and 40% respectively) with fewer patients in the molnupiravir group discontinuing treatment (1.3% vs placebo 3.4%).

3.6.4. Cox et al.; Nature Microbio 6, pg 11–18 (2021)
Preclinical animal data reported significant reductions in viral titre if molnupiravir was administered early after infection as well as suppression of SARS-CoV-2 transmission.

3.6.5. Y Cao et al; IDWeek 2021 Sept 29-Oct 3; Virtual Conference in silico modelling indicated a significant reduction in efficacy if administration was delayed by more than 5 days after infection.

3.7. The Group considered that the safety profile for molnupiravir remains uncertain due to the early stage of the clinical trial programme; however, the Group noted that based on available clinal data there were no reported safety concerns.

3.8. The Group noted that data for the safety of molnupiravir in pregnant people was not available.

3.9. The group noted that data for the safety of molnupiravir in children was not yet available.

3.10. The Group considered the quality of the evidence to be low as trial details were minimal and the findings were unpublished and have not been peer-reviewed. Based on available evidence the Group considered that the current data supported the use of molnupiravir in high risk patients with mild to moderate symptomatic COVID where the oxygen saturation on room air is >93%, i.e. not requiring supplemental oxygen, and treatment has been commenced within 5 days of symptom onset. The Group further noted that the available evidence did not support treatment of hospitalised patients requiring supplemental oxygen.

3.11. In summary the Group considered the strength of the evidence to be high, with a reported absolute reduction in hospitalisation of 6.8% (p=0.0012) and reduction in death rate of 2.1% (MOVe-OUT Phase 3 trial; Unpublished data). Members calculated, using the Fisher exact test, the P-value to be p = 0.003.

3.12. Based on the available evidence the Group considered that it was unlikely that the efficacy of molnupiravir would be affected by COVID-19 specific immunity (either from vaccination or prior exposure). Members considered that it was likely that in the MOVe-Out study there would have been a number of patients with prior viral exposure which was not measured as per trial protocol.

3.13. The Advisory Group noted that the best response to treatment in the clinical data was from 400/800mg daily treatment regimes and that inhibition testing of ribonucleoside N4-hydroxycytidine (NHC) against SARS-CoV-2 variants of concern in the MOVe-IN and MOVe-OUT studies showed equal efficacy. Members considered this was likely due to the mechanism of action being disruptive despite the viral RNA sequence.

3.14. The Advisory Group considered that the populations included in the molnupiravir trials (MOVe-IN and MOVe-OUT) may not be representative of the New Zealand population as there were differing definitions of ‘high risk’ and age cut-offs used, and in addition Māori and Pacific people were not included in the trials.

3.15. The Group concluded that older age was an appropriate factor to consider when assessing clinical risk for a patient but that it should be accounted for alongside other factors such as co-morbidities and Māori or Pacific ethnicity.

3.16. The Group considered that Māori and Pacific people are disproportionality affected by COVID-19; ~27% of current Delta outbreak patients are Māori and ~50% are Pacific people. The Group considered that if the trials had been done in New Zealand then lower age targets, for example 10 years less than that used in the trial protocols, would have been needed to capture these patient groups at high risk of severe illness.

3.17. The Group considered that Māori and Pacific peoples generally have poorer access to health care services, are more likely to live rurally, and often present later for testing. The Group considered that the evidence supports treatment with molnupiravir within 5 days of symptom onset and that this would need to be considered to ensure Māori and Pacific peoples are able to access health care and testing within the timeframe in order to benefit from treatment

3.18. The Advisory Group also considered other published evidence for emerging COVID-19 treatments targeted to mild-moderate disease including the following: REGEN-COV, and COMET ICE.

3.18.1. Weinreich et al; N Engl J Med; [Internet]; 2021 Sep 29
A phase I/II/III randomised double blind trial of REGN-COV (casirivimab and imdevimab) vs placebo.

3.18.2. Gupta et al; COMET-ICE; [Internet]; 2021 Oct 27
A phase III randomised double blind trial of sotrovimab vs placebo in nonhospitalised COVID-19 patients.

3.19. The Group considered the differing population of patients, differing definitions of 'high risk, different age cut-offs and differing endpoints across the COVID-19 therapeutics space makes direct comparisons of efficacy difficult. In general, based on the available evidence, the Group considered that studies with lower ages and less vulnerable patient groups give rise to a higher number to treat (NNT) to prevent hospitalisation or death. Members considered that the data from [MOVe-OUT Phase 3 trial; Unpublished data] indicated an NNT value of 15 for patients hospitalised with COVID-19; whereas REGEN-COV data indicated an NNT of 30-45 for casirivimab/imdevimab for outpatients with COVID-19 and COMET ICE data indicated an NNT of 17 for sotrovimab for non-hospitalised patients with COVID-19.

3.20. The Group considered that although no direct comparisons were available for molnupiravir and casirivimab/imdevimab that it was likely both treatments provide a similar clinical benefit with regards to reduction in hospitalisations. In addition, Members noted that casirivimab/imdevimab needed to be given by infusion/subcutaneous injection and considered that monoclonal antibodies may be less effective against variants with spike protein modifications, as monoclonal antibodies target the spike protein of the virus.

3.21. Members noted that the NZ pricing for molnupiravir and casirivimab/imdevimab was commercially confidential. However, based on suitability of an oral formulation and likely similar efficacy Members considered that molnupiravir may potentially be a more cost-effective treatment for mild-moderate symptomatic COVID-19 than casirivimab/imdevimab in the treatment of mild symptomatic disease in the community.

3.22. The Group considered the safety and efficacy of treating paediatric and pregnant patients with molnupiravir and concluded that there was insufficient data to support it's use in these patient groups.

3.23. The Group considered that the best defence against COVID-19 was vaccination and that this needed to be reiterated with any public communications about the availability of COVID-19 treatments.

3.24. The group considered the use of molnupiravir in combination with other therapies. The group noted that there was no clinical evidence available at this time to support the use of molnupiravir alongside other antiviral treatments or monoclonal antibodies and that limited supplies and high cost would be barriers to any combination treatment.

3.25. The Group considered that should molnupiravir be funded that any unvaccinated patients who are being treated with molnupiravir should be encouraged to get vaccinated.

3.26. The Group considered the non-clinical features of molnupiravir that may impact its use. Members considered that based on the oral presentation of molnupiravir most patients would be able to access molnupiravir via the normal pathways in primary care.

3.27. The Group considered that use of molnupiravir is likely to result in reduced hospital bed-days. The Group considered modelling based on Mayo Clinic real world data (Razonable et al, EClinicalMedicine; Volume 40, October 2021 August 2021) on casirivimab/imdevimab that showed an average bed-day saving of 0.16 days per patient. Members considered that it would be reasonable to assume that bed-day savings would be similar for molnupiravir. However Members cautioned that this was using eligibility based on patients having at least one risk factor, one of which was age >50 years and that the wider the eligibility criteria the lower the likely savings per patient would be.

3.28. The Group considered the below PICO (population, intervention, comparator, outcomes) accurately reflects the intervention in the pivotal phase 3 trial but that consideration for funding is being given to a much wider population – based on the higher hospitalization rates in NZ and, potentially, the disparities in outcomes for Māori and Pacific people infected with the virus.

Table 1: PICO for molnupiravir if it were to be funded in New Zealand for adults with mild to moderate COVID-19 symptoms.

Population	Adults with mild to moderate COVID-19 symptoms (≤5 days from symptom onset) at high risk of progressing to severe disease.
Intervention	Molnupiravir, individual treatment course of 800mg twice daily for 5 days
Comparator(s) (NZ context)	Standard of care
Outcome(s)	Reduced mortality Reduced hospitalisations
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: 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). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

3.29. The Group considered that potential patient numbers going forward are highly uncertain.

3.30. Members considered the epidemiological modelling done by Hendy et al; J Royal Soc NZ; Vol 51 2021; pg s86-s106 assumes a higher case fatality rate than we are currently experiencing (0.7% versus 0.1%) and a lower hospitalization rate (7% versus 9%).

3.31. The Group considered that if we were to continue at 100 new cases per day that would mean around 40,000 cases per annum.

3.32. Members considered that if all those over 40 years of age were treated that would mean about 10,000 per annum, and if other risk factors were added (obesity, diabetes, CKD, COPD, severe heart disease, and cancer) then the number would expand considerably. In addition if Māori and/or Pacific ethnicity were specifically included in the eligibility criteria then the number of treated patients could easily exceed 30,000 per annum.

3.33. Furthermore Members highlighted that if the trials of molnupiravir as a post-exposure prophylactic agent are positive then the numbers of treatment eligible patients could be 3 or 4 times higher.

3.34. The Advisory Group considered that there are ongoing clinical trials investigating the use of molnupiravir, including for the use as a prophylactic treatment of close contacts of positive cases. The Group considered that there could be a health benefit with molnupiravir by targeting prophylactic treatment to close contacts who are at risk of severe illness and that it would be willing consider this indication once more evidence becomes available.

3.35. The Advisory Group noted that based on international experience prophylactic treatment of case contacts would increase the required number of doses by at least 3-4 times over treating only COVID-19 positive patients and that due to extremely high demand internationally supplies available in Aotearoa New Zealand could be limited.

Casirivimab and imdevimab for the treatment of COVID-19

1. Application

1.1. The Advisory Group considered material provided by the Supplier and Pharmac staff regarding casirivimab and imdevimab for 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 acknowledged that based on available evidence there are four distinct patient populations which may benefit from treatment with casirivimab and imdevimab.

2.1.1. Seronegative patients in hospital with mild to moderate COVID-19 who do not require supplemental oxygen.
2.1.2. Patients in the community with mild to moderate symptomatic COVID-19 at risk of progressing to severe disease
2.1.3. Treatment of asymptomatic COVID-19 in the community,
2.1.4. Close contacts of positive cases >48 hours who are at risk of severe disease.

2.2. The Advisory Group **recommended** that casirivimab and imdevimab be funded in hospital (in the Hospital Medicines List) for the treatment of mild to moderate-symptomatic COVID-19, subject to the following eligibility criteria.

Restricted
Indication – mild to moderate COVID-19-hospitalised patients

Any relevant practitioner.
Therapy limited to max dose of 2400 mg
All of the following:

1. Patient is an in-patient in hospital with mild to moderate disease severity*; and
2. Patient has confirmed (or probable) COVID-19; and
3. Patient's symptoms started within the last 10 days; and

4. Patient is not receiving high flow oxygen or assisted/mechanical ventilation; and
5. Either:
   (a) Age > 50; or
   (b) BMI >30; or
   (c) Patient is at increased risk of severe illness from COVID-19, excluding pregnancy, as described on the Ministry of Health website; and
6. Either:
   a) Patient is unvaccinated; or
   b) Patient is seronegative

Note:* Mild to moderate disease severity as described on the Ministry of Health Website

2.3. The Advisory Group **recommended** that casirivimab and imdevimab be funded in the community (Section B of the Pharmaceutical Schedule) for the treatment of mild to moderate symptomatic COVID-19, subject to the following eligibility criteria:

Restricted
Indication – Treatment of profoundly immunocompromised patients in the community
Any relevant practitioner.
Therapy limited to max dose of 2400 mg
1) All of the following:
   1. The patients is in the community
   2. Patient has confirmed (or probable) COVID-19; and
   3. Either:
      a) Patient is profoundly immunocompromised** and is at risk of not having mounted an adequate response to vaccination against COVID-19, or
      b) Patient is profoundly immunocompromised** and is unvaccinated; and
   4. Patient's symptoms started within the last 10 days; and
   5. Patient is not receiving high flow oxygen or assisted/mechanical ventilation

Note:* Mild to moderate disease severity as described on the Ministry of Health Website

** Examples include B-cell depletive illnesses or patients receiving treatment that is B-Cell depleting,

2.4. The Advisory Group **recommended** that casirivimab and imdevimab not be funded for for the treatment of patients in the community with symptomatic COVID-19 who have risk factors for progressing to severe disease based on the limited supply of casirivimab and imdevimab, high numbers needed to treat in this community setting and that molnupirivir is likely a better option for these patients given the potential logistical difficulties associated with community administration.

2.5. The Advisory Group **recommended** that casirivimab and imdevimab not be funded for the treatment of the wider group of patients in the community with asymptomatic COVID-19, or mild COVID-19 who do not have significant risk factors for progressing to severe disease, based on the limited supply of casirivimab and imdevimab, and high numbers needed to treat in this community setting.

2.6. The Advisory Group **recommended** that casirivimab and imdevimab not be funded for the treatment of close contacts of positive cases. on the basis of the low strength of evidence for the use of casirivimab and imdevimab in this setting.

2.7. In making these recommendations, the Advisory Group considered the high health need and the lack of treatment options for patients with mild to moderate COVID-19, and immunocompromised people who are either unable to mount a response to vaccination against COVID-19 or are unvaccinated. The Advisory Group also considered the equity implications of COVID-19 and likelihood of a higher mortality rate for patients with comorbidities, the safety and efficacy profile of casirivimab and imdevimab for COVID-19 and likely measurable health benefits.

2.8. The Advisory Group noted casirivimab and imdevimab has been developed specifically for the treatment of COVID-19 and is currently under assessment by Medsafe. The Group noted that is has been approved for use in overseas jurisdictions including Australia, Canada, Japan, the United States of America, the United Kingdom and Europe.

2.9. 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.

2.10. 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 Group noted that there are two pharmaceuticals explicitly funded for treatment of COVID-19 in Aotearoa New Zealand, tocilizumab and remdesivir. The Advisory Group further noted that tocilizumab and remdesivir are funded for the treatment of moderate to severe COVID-19 and that apart from steroids there are currently no treatments funded for mild COVID-19 in New Zealand.

3.2. The Group noted that casirivimab and imdevimab is an investigational treatment that consists of 2 monoclonal antibodies (casirivimab and imdevimab) that bind to two different sites of the SARS-CoV-2 spike protein. Binding to the spike proteins prevents the virus from binding to the ACE receptor, thereby blocking virus entry into cells.

3.3. The Group considered clinical evidence for casirivimab and imdevimab for the treatment of mild-moderate COVID-19.

3.3.1. Post exposure prophylaxis: O'Brien, et al. N Engl J Med 2021; 385:1184-1195

A two-part, randomized, double-blind, placebo-controlled trial evaluating casirivimab and imdevimab (Ronapreve) in household contacts of people with COVID-19. Participants (≥12 years of age) who were enrolled within 96 hours after a household contact received a diagnosis of SARS-CoV-2 infection, were randomly assigned, in a 1:1 ratio, to receive a total dose of 1200 mg of casirivimab and imdevimab or matching placebo administered by means of subcutaneous injection. Symptomatic SARS-CoV-2 infection developed in 11 of 753 participants in the casirivimab and imdevimab group (1.5%) and in 59 of 752 participants in the placebo group (7.8%) (relative risk reduction [1 minus the relative risk], 81.4%; P<0.001). Number needed to treat (NNT) to prevent 1 extra symptomatic SARS-Cov-2 infection within 28 days was 16.
In weeks 2 to 4, a total of 2 of 753 participants in the casirivimab and imdevimab group (0.3%) and 27 of 752 participants in the placebo group (3.6%) had symptomatic SARS-CoV-2 infection (relative risk reduction, 92.6%). Casirivimab and imdevimab also prevented symptomatic and asymptomatic infections overall (relative risk reduction, 66.4%). Among symptomatic infected participants, the median time to resolution of symptoms was 2 weeks shorter with casirivimab and imdevimab than with placebo (1.2 weeks and 3.2 weeks, respectively).

3.3.2. Early treatment of asymptomatic disease in the community O'Brien et al .N Engl J Med. 2021 Sep 23;385(13):1184-1195

A two-part, randomized, double-blind, placebo-controlled trial evaluating casirivimab and imdevimab in recently infected asymptomatic patients with COVID-19. Participants (≥12 years of age) who were enrolled within 96 hours after a household contact received a diagnosis of SARS-CoV-2 infection were randomly assigned, in a 1:1 ratio to receive a total dose of 1200 mg of casirivimab and imdevimab or matching placebo administered by means of subcutaneous injection. The study reported subcutaneous casirivimab and imdevimab 1200mg significantly prevented progression from asymptomatic to symptomatic disease compared with placebo 31.5% relative risk reduction (P=.0380) and a 6-day reduction in symptom duration per symptomatic participant.
Treatment-emergent adverse events were 48.1% compared with 33.5% for those receiving casirivimab and imdevimab including events related to and not related to COVID-19. The proportion of participants receiving placebo who had ≥1 treatment-emergent adverse events was 48.1% compared with 33.5% for those receiving casirivimab and imdevimab, including events related (39.7% vs 25.8%, respectively) or not related (16.0% vs 11.0%, respectively) to COVID-19.

3.3.3. Treatment in hospitalised patients with COVID-19 – Platform study. Horby, et al. MedRxiv 2021;258542 (a pre-peer reviewed publication)

A randomized, controlled, open-label platform trial evaluating casirivimab and imdevimab in patients hospitalised with COVID-19. 9785 patients were randomly allocated to receive usual care plus casirivimab and imdevimab or usual care alone, including 3,153 (32%) seronegative patients, 5,272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status. Eligible patients were randomly allocated (1:1) to either usual standard of care alone or usual care plus a single dose of casirivimab and imdevimab 8000 mg by intravenous infusion (REGEN-COV group). The primary outcome was 28-day mortality assessed first among patients without detectable antibodies to SARS-CoV-2 at randomisation (seronegative) and then in the overall population. The study reported a reduction in mortality compared with placebo 24% vs 30% for seronegative patients (NNT = 17). Mortality differed significantly between seropositive and seronegative patients (p value for heterogeneity = 0·001). No meaningful differences in mortality at 28 days were observed between the casirivimab and imdevimab and usual care groups in seropositive patients. The mean age of study participants in this comparison was 61.9 years (SD 14.5) and the median time since symptom onset was 9 days (IQR 6 to 12 days)

3.3.4. Treatment in hospitalised patients with symptomatic COVID-19. Study 2066

An Ongoing, randomized, double-blind, placebo-controlled, seamless Phase 1/2/3 study evaluating casirivimab and imdevimab in hospitalized patients with COVID-19. Cohort 1 (low flow oxygen) results reported that seronegative patients (n= 217) treated with casirivimab and imdevimab had a lower risk of death or mechanical ventilation compared with those treated with placebo (n=270). Seropositive patients receiving casirivimab and imdevimab demonstrated limited clinical benefit compared with seropositive patients receiving placebo.

3.3.4.1. The Group noted that further enrolment into Cohort 2 (patients on high-intensity oxygen) and Cohort 3 of Study 2066 (patients on mechanical ventilation) was stopped following a potential safety signal and an unfavourable risk/benefit profile in these patients.

3.3.4.2. The Group noted that similar clinical and virologic efficacy was observed for the patients administered 8000 mg and 2400 mg doses of casirivimab and imdevimab.

3.3.5. Treatment in community patients with symptomatic COVID-19, at risk of progressing to severe disease. Weinreich DM et al. N Engl J Med. 2021 Sep 29 A randomized, double-blind, placebo-controlled, phase 1/2/3 master protocol evaluating the casirivimab and imdevimab in outpatients with one or more risk factors for severe COVID-19. Participants included 4,057 COVID-19 outpatients with one or more risk factors for severe disease. Risk factors included age >50 yrs, BMI > 30, cardiovascular disease, chronic lung disease, diabetes, chronic kidney disease, chronic liver disease and immunosuppressed. Patients were randomized to a single treatment of intravenous placebo, or 2400 mg or 1200 mg doses of casirivimab and imdevimab, within 7 days of symptom onset and were followed for 28 days. The authors reported significantly reduced COVID-19-related hospitalization or all-cause death compared to placebo (2.4 gm: 71.3% reduction [1.3% vs 4.6%; p<0.0001], NNT-30 and 1.2 gm: 70.4% reduction [1.0% vs 3.2%; p=0.0024], NNT-45). The median time to resolution of COVID-19 symptoms was 4 days shorter in both dose arms vs placebo (10 vs 14 days; p<0.0001). Efficacy of casirivimab and imdevimab was consistent across subgroups, including patients who were SARS-CoV-2 serum antibody-positive at baseline. Serious adverse events occurred more frequently in the placebo group (4.0%) than in the 1200mg (1.1%) and 2400mg (1.3%) groups and grade ≥2 infusion-related reactions were infrequent (<0.3% in all groups).

3.3.6. Copin et al. Cell. 2021;184:3949:3961

A clinical trial to investigate the sequence diversity of the spike protein and monitored emergence of virus variants in SARSCOV-2 isolates found in COVID-19. Casirivimab and imdevimab was evaluated against variants of concern as defined by the Centers for Disease Control and Prevention (CDC), including B.1.1.7 (UK), B.1.427/B.1429 (California), B.1.351 (South Africa), P.1 (Brazil), B.1.526 (New York), and B.1.617.1/B.1.717.2/B.1.617.3 (India) lineages. The authors reported that the combination of non-competing antibodies in casirivimab and imdevimab provides protection against all current SARS-CoV 2 variants of concern and also protects against emergence of new variants and their potential seeding into the population in a clinical setting.

3.3.7. Razonoble et al. EClinicalMedicine. 2021 Aug 30;101102

A retrospective study to assess the outcomes of casirivimab imdevimab treatment of mild to moderate COVID-19. Participants were adult (18 years old) patients identified from the Mayo Clinic EHR database with positive SARS-CoV-2 PCR tests between December 4, 2020 and April 9, 2021. The participant selection algorithm resulted in two cohorts that were balanced for relevant demographic and clinical covariates: (1) treated patients who received casirivimab imdevimab infusion, and (2) control patients who did not receive anti-spike monoclonal antibody after diagnosis of COVID-19.

The authors reported all-cause hospitalisation rates at day 14 of 1.3% vs 3.3%; ((absolute difference: 2.0%; 95% confidence interval (CI):0.5-3.7%)), day 21 1.3% vs 4.2%; (absolute difference: 2.9%; 95% CI: 1.2-4.7%), and day 28 1.6% vs 4.8%;(Absolute Difference: 3.2%; 95% CI: 1.4-5.1%). Rates of intensive care unit admission and mortality at days 14, 21 and 28 were similarly low for antibody-treated and untreated groups. Adverse events were uncommon and mild. There were low rates of all-cause mortality and ICU admission in both the treated and untreated populations.

3.3.8. The Group noted a September 2021 Cochrane living systematic review of SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19 (Krezberger et al. CDSR,2021,9CDO13825). The authors concluded that the certainty of evidence for use in all non-hospitalised individuals was low, and was very low to moderate in hospitalised individuals. The authors considered the current evidence was insufficient to draw meaningful conclusions regarding treatment with SARS-CoV-2-neutralising mAbs. The Group noted this review did not include the most recent studies, and considered that this is a rapidly evolving area and data continues to emerge in this space.

3.4. The Group noted that a number of studies have reported that COVID-19 variants that contain the E848K mutation display significant resistance to the efficacy of neutralizing monoclonal antibodies.

3.5. The Group considered the treatment paradigm for COVID-19 and that based on the available evidence that casirivimab and imdevimab would be used before currently funded treatments (remdesivir and tocilizumab) for moderate to severe COVID-19.

3.6. The Group considered that based on available evidence there were four distinct patient populations which may benefit from treatment with casirivimab and imdevimab.
   3.6.1. Seronegative patients in hospital with mild to moderate COVID-19 who do not require supplemental oxygen with an approximate Number Needed to Treat (NNT) of 14 to prevent one death.
   3.6.2. Patients in the community with mild COVID-19 at risk of progressing to severe illness with an approximate NNT of 30 to prevent one extra hospitalisation or death.
   3.6.3. Patients in the community with asymptomatic disease (study on-going).
   3.6.4. Close contacts of positive cases >48 hours who are at risk of severe illness with an approximate NNT of 11 to prevent one individual developing symptomatic or asymptomatic COVID-19 infection .

3.7. The Group considered within the wider community group with mild symptomatic disease, there was a subgroup of patients with a particular high health need; the group of profoundly immunocompromised people who are unable to mount a response to vaccination, or who have not been vaccinated against COVID-19. The Group considered this group had the highest need for treatment with casirivimab imdevimab in the community setting. Members considered that this patient group is likely to be small.

3.8. The Group noted probable class effects between casirivimab and imdevimab and other neutralising monoclonal antibodies for the treatment of COVID-19 and considered that the strength and quality of the evidence for the health benefits that may be gained from treatment with casirivimab and imdevimab varied across the different treatment settings.
   3.8.1. The Group considered that the quality of the available evidence was good and was of a modest strength for use of casirivimab and imdevimab in patients hospitalised with mild to moderate COVID-19.
   3.8.2. The Group considered that the quality of the available evidence was good and was of a modest strength for use of casirivimab and imdevimab in patients in the community with mild to moderate COVID-19 at high risk of progressing to severe illness.
   3.8.3. The Group considered that the quality and strength of the available evidence was moderate for use of casirivimab and imdevimab in post-exposure

prophylactic treatment of patients at risk of infection with COVID-19, but were uncertain how this would impact subsequent hospitalisation and/or death.

3.9. The Group discussed that casirivimab and imdevimab was required to be administered via IV infusion or subcutaneous injection. However Members noted that if given via subcutaneous injection, four, 2.5ml injections were required which may be difficult for some people. The Group considered that administering casirivimab and imdevimab via IV infusion or subcutaneous injection in the community would be resource intensive and the resource and infrastructure required to deliver this, particularly in rural communities, may be limited in some areas of New Zealand.

3.10. The Group considered that the trial populations were probably not representative of the New Zealand population as the severity threshold for admitting people to hospital in New Zealand appeared to currently be lower than that of other countries; for example a mild to moderate hospitalised person in New Zealand was currently likely less severe than a mild to moderate hospitalised person in the United Kingdom. The Group considered that patients in New Zealand may be hospitalised with mild to moderate disease (as opposed to being cared for in the community) due to comorbidities that put them at risk of severe illness. Members considered that doses of 1200 mg were used in these trial populations (albeit in community setting in the trials) and considered this would be appropriate for inclusion in the eligibility criteria.

3.11. The Group noted the results published by Weinreich DM et al. N Engl J Med. 2021 Sep 29; 2400mg and 1200mg significantly reduced COVID-19-related hospitalization or all-cause death compared to placebo (71.3% reduction [1.3% vs 4.6%; p<0.0001] and 70.4% reduction [1.0% vs 3.2%; p=0.0024], respectively) and The median time to resolution of COVID-19 symptoms was 4 days shorter in both dose arms vs placebo (10 vs 14 days; p<0.0001). Members considered the outcomes were similar between the 1200mg and 2400mg dosing and therefore 1200 mg dosing was appropriate for use in the mild to moderate setting.

3.12. The Group considered the draft data sheet provided by the Supplier indicated that casiribimab and imdevimab at a dose of 1200mg had been submitted to the regulator for the treatment of confirmed COVID-19 in patients aged 12 years and older and weighing at least 40 kg, that do not require supplemental oxygen for COVID-19, and who are at high risk of progressing to severe COVID-19.

3.13. The Group considered, based on Weinreich DM et al. N Engl J Med. 2021 Sep 29 that it was uncertain whether there was a health benefit for use of doses greater than 2400 mg; i.e. 8000mg, for hospitalised patients in New Zealand with severity beyond the mild to moderate setting but would be happy to review this again should further evidence become available.

3.14. The Group noted that the currently recommended dosing of casirivimab and imdevimab is 600 mg casirivimab and 600 mg imdevimab (1200 mg total dose); however; dosing in the clinical trials that were considered by the Group ranged from 1,200 mg to 8,000 mg in patients with more severe disease receiving higher doses than those with more mild disease. The Group considered dosing higher for the treatment of patients with more severe COVID-19 would impact the number of patients able to be treated with the doses of casirivimab and imdevimab secured by Pharmac would be reduced. The Group noted the results of Study 2066 and considered that to preserve supply for as many patients as possible it may be appropriate to limit dosing to 2400 mg per patient.

3.15. The Advisory Group noted the emergence of antiviral treatments for the treatment of mild to moderate COVID-19 including molnupiravir and PF-07321332, which can be administered orally. The Group considered that these treatments could provide a more suitable alternative treatment options for patients with mild to moderate COVID-19 in the community.

3.16. The Group considered that on balance of the information provided the serostatus of a patient at the time of treatment with casirivimab and imdevimab appeared to be particularly important for predicating whether a patient would benefit from treatment with casirivimab and imdevimab in hospitalised patient with mild-moderate symptomatic COVID-19. The Group considered the practical implications of this for the New Zealand Health Sector and noted it would require the availability of a rapid antibody assay for testing serostatus prior to treatment being administered. The Group noted access to this testing is not widely available in New Zealand and were uncertain if it would be available in the near future.

3.17. The Group noted that the current COVID-19 outbreak in New Zealand was largely being experienced by unvaccinated people and considered based on this it would be reasonable to assume, in the New Zealand population, that an unvaccinated person infected with COVID-19 could be assumed to be seronegative for the purposes of treatment with casirivimab and imdevimab being administered in hospitalised patients with mild-moderate symptomatic COVID-19.

3.18. The Group considered the health need of patients hospitalised with mild to moderate COVID-19 is high and noted both unvaccinated and Māori and Pacific populations as those with high risk factors for developing moderate-severe COVID-19. For Māori; lower vaccination rates, higher risk of developing severe COVID due to comorbidities (diabetes, obesity, CVS disease, respiratory disease) and delayed presentation were considered to increase the risk of progressing to moderate to severe COVID-19.

3.19. The Group noted that New Zealand data indicates that Māori are overrepresented in terms of COVID-19 incidence and hospitalisation in New Zealand. Members noted a 2020 study combining existing demographic and health data for ethnic groups in New Zealand to estimate inequities in COVID-19 infection fatality rates (IFR) in New Zealand by ethnicity (Steyn et al. N Z Med J. 2020;133:28-39). The group noted that this study estimated infection mortality rate for Māori could be 50% higher than that of non-Māori and considered this could be even higher depending on the relative contributions of age, residence (including household composition and crowding) and underlying health conditions to mortality risk from COVID-19. The Group further considered that Pacific populations share similar co-morbidity profiles etc. to Māori and would therefore also potentially have similarly higher fatality rates than NZ European cohorts.

3.20. The Group considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for casirivimab and imdevimab if it were to be funded in New Zealand for treatment of COVID-19. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Group's assessment at this time. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff:

3.21. **Table 1:** PICO for casirivimab and imdevimab if it were to be funded in New Zealand for mild to moderate COVID-19.

Population	1) In-patients hospitalised with mild to moderate COVID-19 2) Profoundly immunocompromised patients in the community
Intervention	1200 mg casirivimab and imdevimab (max dose 2400 mg per patient)
Comparator(s) (NZ context)	Standard of care
Outcome(s)	Reduced mortality Reduced time to recovery Reduced days in hospital

Table definitions:

Population: 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.

3.22. The Group considered there was significant uncertainty regarding the number of patients in New Zealand who may require treatment with casirivimab and imdevimab and considered that worst case scenario modelling of SARS-COV-2 infection (based on modelled Auckland figures of 5,300/week) suggests there could be approximately 13,900 new cases/week resulting in 900 hospital admissions per week.

3.23. The Group considered there is variation in the evidence between estimated contacts, close contacts and social contacts and how these are defined and whether the definitions of each are relevant to the definition of a close contact, casual plus contact and casual contact outlined by the Ministry of Health. The Group considered available evidence which suggests the number of close contacts for individuals with SARS CoV-2 could range from 2.1 - 5.1 depending on the restrictions in place McAloon et al, 2021. The Group noted that this study was undertaken in Ireland and may not reflect the New Zealand population.

3.24. The Group considered that it was important that if casirivimab and imdevimab were to be funded that it did not negatively impact the Government's COVID-19 vaccination programme.

Baricitinib for treatment of moderate-severe COVID-19

1. Application

1.1. The Advisory Group considered a paper from Pharmac staff regarding baricitinib for treatment of moderate-severe COVID-19.

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

1.3. The Advisory Group **recommended** that baricitinib be funded for the treatment of moderate-severe COVID-19, subject to the following Special Authority / Hospital Restriction criteria.

Restricted
Indication – moderate to severe COVID-19*

Any relevant practitioner.
Therapy limited to 14 days.
All of the following:

1. Patient has confirmed (or probable) COVID-19; and
2. Oxygen saturation of <92% on room air, or requiring supplemental oxygen; and
3. Patient has significantly increased laboratory markers of systemic inflammation (eg CRP, procalcitonin or ferritin); and
4. Patient is receiving adjunct systemic corticosteroids, or systemic corticosteroids are contraindicated; and
5. Baricitinib is to be administered at doses no greater than 4mg daily for up to 14 days; and
6. Baricitinib is not to be administered in combination with tocilizumab.

Note: *Baricitinib is an unapproved medicine supplied under Section 29

1.4. In making this recommendation, the Advisory Group considered the high health need and limited treatment options for patients with moderate to severe COVID-19, the equity implications of COVID-19 and likelihood of a higher mortality rate for patients with comorbidities, the safety and efficacy profile of baricitinib when used concomitantly with systemic corticosteroids for COVID-19 and likely measurable health benefits.

1.5. Members noted baricitinib is approved for use in rheumatoid arthritis and atopic dermatitis in Australia but is unapproved for use in New Zealand in any indications. However the Group considered that baricitinib would be a suitable clinical alternative to tocilizumab for the treatment of moderate-severe COVID-19 where tocilizumab is not available/in limited supply.

1.6. The 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.

1.7. 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.

3.1. The Advisory Group noted that there are two pharmaceuticals explicitly funded for treatment of COVID-19 in Aotearoa New Zealand, tocilizumab and remdesivir. The Group further noted that the primary consideration for use of baricitinib was as a potential substitute for tocilizumab in the treatment of moderate-severe COVID-19 due to the worldwide shortage of tocilizumab.

3.2. The Group considered that securing a supply of baricitinib could allow Aotearoa New Zealand's remaining tocilizumab stock to be reserved for patients who do not have access to a funded alternative.

3.3. The Group noted that baricitinib is a janus kinase (JAK) inhibitor typically used to treat rheumatoid arthritis via inhibition of IL-6-induced STAT3 phosphorylation. The anti-inflammatory action of both tocilizumab and baricitinib was considered to be the primary method of action for COVID-19 treatment.

3.4. The Group noted that inflammatory response and related lung injury associated with SARS-CoV2 (COVID-19) has been the subject of interest and research since the emergence of SARS-CoV2, leading to the investigation of the inflammatory markers

thought to be up-regulated in patients with moderate to severe COVID-19 as clinical predictors of mortality.

3.5. The Group considered JAK-inhibitors should be considered for use prior to multiorgan dysfunction;1-2 weeks of disease (Limen et al. Expert Rev Anti Infect Ther. 2021: 1–10)

3.6. The Group noted that while baricitinib was not approved by Medsafe for any indication it was subject to a FDA emergency use authorisation and recommended by other jurisdictions, including Australia and the United States, as part of their COVID-19 treatment guidelines.

3.7. The Group considered the clinical evidence for baricitinib for the treatment of moderate-severe COVID-19. The group noted two primary studies, a meta-analysis on JAK inhibitors for COVID-19 and preclinical evidence for the use of baricitinib for COVID-19. In addition, the Group considered that as tocilizumab has a similar mechanism of action to baricitnib that studies investigating tocilizumab for the treatment of COVID-19 could be used to cautiously inform the interpretation of the baricitinib data.

3.7.1. Kalil AC et al. N Eng J Med. 384: 795-807

A double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir (without systemic corticosteroids) in hospitalized adults with Covid-19. The study reported an improvement in clinical status at day 15, however there was no improvement in 28 day mortality. The authors conducted further sub-group analysis and reported patients receiving high-flow oxygen or non-invasive ventilation at enrolment had a time to recovery of 10 days with combination treatment and 18 days with control.

3.7.1.1. The Group considered that a particular limitation of the study was that mortality was followed only to 28 days and that 60 days would have been more informative. In addition no information about long term sequelae was captured.

3.7.1.2. The Group considered that no increase in serious adverse events in the treatment arm was reported and that there was a small reduction in adverse events in the treatment arm reported.

3.7.2. Marconi VC. (COV-BARRIER): Lancet Resp Med [Online]. 1 Sep 2021

A Phase 3, double-blind, randomised, placebo-controlled trial evaluating baricitinib 4mg daily vs placebo. Standard of care included systemic corticosteroids and antivirals such as remdesivir. The authors of the study reported no reduction in the frequency of disease progression. However there was a reduction in 28 and 60 day all-cause mortality reported with a Numbers Needed to Treat (NNT) of 20.

3.7.2.3. The Group considered that the reduction in mortality at both 28 and 60 days was clinically meaningful. In addition Members further considered that the overall positive effects seem to be greater when combined with dexamethasone as was noted in studies with tocilizumab + steroids (REMAP-CAP/RECOVERY trials).

3.7.2.4. The Group considered that no increase in serious adverse events in the treatment arm was reported and that there was a small reduction in adverse events in the treatment arm.

3.7.3. Limen RY et al. Expert Rev Anti Infect Ther 2021 : 1-10
A systematic review and meta-analysis of the use of JAK inhibitors to treat COVID-19. The authors of the study reported that there is evidence that treatment of hospitalised COVID-19 patients with JAK inhibitors (baricitinib, ruxolitinib, tofacitinib) corresponded with increased recovery rate, shorter time to recovery and decreased mortality rate.

3.7.4. Hoang TN et al. Cell. Jan 21; 184(2): 460–475.e21
A preclinical trial in a rhesus macaque model of SARS-CoV2 infection showed no antiviral effect from baricitinib but demonstrated reduced inflammation, decreased lung infiltration of inflammatory cells and more limited lung pathology.

3.8. Overall, the Group considered the strength of evidence supporting baricitinib for moderate-severe COVID-19 as moderate to low. The Group considered that based on reviewed evidence, baricitinib possibly reduces mortality, length of hospital stay and time to recovery in those with COVID-19 who are developing the inflammatory response.

3.9. Members considered that the completed trials used non-standard matrices for intensive care results, were carried out prior to the current standard of care and before the COVID-19 Delta variant was prevalent. However, due to the high health need of patients with moderate to severe COVID-19 and on the basis of the clinical evidence that was reviewed, the Group was supportive of baricitinib being a funded option for the treatment of COVID-19.

3.10. The Group considered the clinical evidence for tocilizumab. In particular Members considered the REMAP-CAP/RECOVERY trials reported a benefit of tociluzumab use when combined with corticosteroids. The Group considered it was reasonable to assume the potential for a similar effect with baricitinib and other JAK inhibitors. The group noted JAK inhibitors ruxolitinib and tofacitinib could be treatments for further investigation.

3.11. The Group considered that systemic corticosteroids can inhibit the IL-6 pathway in COVID-19 patients, and that the degree of inhibition has prognostic importance. The Group considered systemic corticosteroids are an important driver of reduction in symptom burden, hospital stay, and mortality. For this reason, Members considered that it was important that use of tocilizumab or baricitinib should be in conjunction with corticosteroids where possible.

3.12. The Group considered that there was no available evidence to suggest that baricitinib should be used in combination with tocilizumab and due to similar mechanisms of action it would only be clinically appropriate to use one or the other.

3.13. The Group considered that of the evidence considered (Marconi VC. (COV-BARRIER): Lancet Resp Med [Online]. 1 Sep 2021 and Kalil AC et al. N Eng J Med. 384: 795-807) baricitnib was investigated at doses of 4 mg once daily for a duration

of up to 14 days and therefore if baricitinib was to be funded that should be limited to this dosage.

3.14. The Group considered the pharmacokinetics of baricitinib and noted that it is primarily cleared by renal elimination. (Jorgensen et al. Pharmacotherapy. 2020;40:843-856).

3.14.1. Members considered that dosing reductions would therefore be required for those with renal impairment and that treatment with baricitinib may not be appropriate for those with severe renal impairment. Members considered that dosage reductions would be required for children, however the Group considered there was insufficient clinical evidence regarding the safety of baricitinib in paediatric patients. In addition the Group considered there was insufficient clinical evidence for safety of baricitinib in pregnancy.

3.14.2. The Group noted the half-life of baricitinib was significantly shorter than that of tocilizumab. The Group considered that this could be a potential advantage over tocilizumab for some patients due to the ability to discontinue use if clinical circumstances changed.

3.15. The group considered the patient population most likely to benefit to be very similar to that of tocilizumab. Members considered that there was significant uncertainty regarding potential patient numbers due to the difficulty modelling future projections for COVID-19 cases in NZ. Members considered that a reasonable estimate could be approximately 4% of symptomatic COVID-19 cases may require tocilizumab or baricitinib.

3.16. The Group considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for baricitinib if it were to be funded in New Zealand for treatment of COVID-19. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Group's assessment at this time. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff:

Table 1: PICO for baracitinib if it were to be funded in New Zealand for moderate-severe COVID-19.

Population	Patients hospitalised with moderate/severe COVID-19
Intervention	Baricitinib 4mg daily
Comparator(s) (NZ context)	Standard of care
Outcome(s)	Reduced mortality Reduced time to recovery Reduced days in hospital
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: 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.

3.17. The Group considered the health need of patients with moderate-severe COVID-19 as very high and noted both unvaccinated and Māori and Pacific populations as those with high risk factors for moderate-severe COVID-19. For Māori; lower vaccination rates, higher risk of developing severe COVID due to comorbidities (diabetes, obesity, CVS disease, respiratory disease) and delayed presentation were considered to increase the risk of moderate/severe COVID-19.

3.18. The Group considered the non-clinical features of baricitinib (tablet formulation) and noted that it could either be swallowed or dissolved in water for those patients who are unable to swallow.

3.19. The Advisory Group considered that overall baricitinib was likely to be a suitable substitute for tocilizumab for the treatment of moderate-severe COVID-19 but the overall quality of evidence was poor to moderate. The Group considered that tocilizumab was the preferred treatment as the quality of evidence for tocilizumab was slightly better. However, it was noted that tocilizumab may not be available due to global shortages.

3.20. The Group considered it would be appropriate to have the same eligibility criteria for baracitinib as tocilizumab. Members considered that the word 'significantly', used in the criteria to describe the level of increased inflammatory markers may not be necessary, as clinicians are able to determine whether inflammatory markers are increased based on clinical judgement. However, Members considered that if this was to be removed then it should also be removed from the tocilizumab criteria.