Record of the Ad-hoc Covid Treatments Advisory Group Meeting held on 13 December 2021

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.

Present
Jane Thomas
Brian Anderson
Tim Cutfield
Eamon Duffy
Gillian Hood
Jessica Keepa
Stephen Munn
Marius Rademaker
Nigel Raymond
Justin Travers

Casirivimab and imdevimab for the treatment of COVID-19 in the community

Application

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

Recommendation

1.2. The Advisory Group **recommended** casirivimab and imdevimab be funded, subject to Medsafe approval, for the treatment of mild to moderate COVID-19 in the community subject to the following access criteria:

Initial Application – (Acute COVID-19 disease) Any relevant practitioner. Approvals valid for 2 weeks for all applications meeting the following criteria:
Any relevant practitioner.
Therapy limited to maximum dose of 2400 mg.

All of the following:

1. Patient is in the community
2. Patient has confirmed (or highly suspected) COVID-19;
3. Patient's symptoms started within the last 10 days;
4. Patient is not receiving supplemental oxygen or assisted/mechanical ventilation, and
5. Either:
   - 5.1. Patient is unvaccinated; or
   - 5.2. Patient is seronegative where serology testing is readily available or strongly suspected to be seronegative where serology testing is not readily available; and
6. Any of the following:
   - 6.1. Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection*; or
   - 6.2. All of the following:
     - 6.2.1. Patient is Māori or any Pacific ethnicity; and
     - 6.2.2. Patient is aged 50 years or more; and
     - 6.2.3. Patient has at least one additional risk factor for severe COVID-19**; OR
   - 6.3. Both:
     - 6.3.1. Patient is Māori or any Pacific ethnicity; and
     - 6.3.2. Patient has at least two additional risk factors for severe COVID-19**; or
   - 6.4. Both:
     - 6.4.1. Patient is aged 50 years or more; and
     - 6.4.2. 9.2 Patient has at least two additional risk factors for severe COVID-19** or;
7. Patient has at least three risk factors for severe COVID-19**

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

**Patients at risk of severe illness from COVID-19, as described on the Ministry of Health website

1.3. 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 it did not need to discuss a priority ranking.

1.4. 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.

Discussion

1.5. The Advisory Group noted that it had considered casirivimab and imdevimab for the treatment of COVID-19 at its 21 October 2021 meeting, which resulted in recommendations for funding for patients hospitalised with mild to moderate COVID-19 and funding in the community for profoundly immunocompromised patients.

1.6. The Advisory Group noted that at its 21 October 2021 meeting, it had not recommended casirivimab and imdevimab for funding for the treatment of patients in the community with symptomatic COVID-19 who have risk factors for progressing to severe disease. The Advisory Group noted that at the time of its 21 October 2021 meeting this recommendation was made due to the limited volume of casirivimab and imdevimab available, the high numbers of patients needed to treat (NNT) in this setting to prevent one hospitalisation or death, and that oral antiviral treatments are likely a more suitable option for these patients given the potential logistical difficulties associated with community administration of parenterally administered monoclonal antibody treatments.

1.7. The Advisory Group noted that following its 21 October 2021 meeting members had had a discussion regarding the additional high-risk patient groups in the community, including Māori and Pacific peoples and other populations experiencing health disparities who may benefit from treatment with casirivimab and imdevimab. In making these recommendations the members noted that while oral antiviral treatments may be a more suitable treatment for use in the community, casirivimab and imdevimab was expected to arrive in New Zealand before oral antiviral treatments and could be used to treat vulnerable patients before oral antivirals are available.

1.8. The Advisory group noted that following its 21 October 2021 meeting Pharmac had secured an additional supply of 7,500 1200 mg doses of casirivimab and imdevimab for the 2022 calendar year. It was anticipated that this would provide sufficient stock for the treatment of profoundly immunocompromised patients and patients hospitalised with mild to moderate COVID-19, which had already been recommended by the Advisory Group for funding and would provide some flexibility for treating other patient groups at severe risk of COVID-19.

1.9. The Advisory Group noted the limited volume of casirivimab and imdevimab available and considered it would be important to target access to people who would benefit most and to ensure that demand for casirivimab and imdevimab did not exceed the supply available.

1.10. The Advisory Group noted the risk factors for a person progressing to severe COVID-19 including information available on the Ministry of Health website and considered it provided a reasonable indication of risk factors for severe COVID-19.

1.11. The Advisory Group considered the following clinical evidence for casirivimab and imdevimab for the treatment of patients in community settings:

1.11.1. Weinreich DM et al. N Engl J Med. 2020 Dec 17 Interim analysis of a randomized, double-blind, placebo-controlled, phase 1–3 clinical trial involving symptomatic, non-hospitalized patients with confirmed Covid-19 (phase 1-2 portion of the trial) which evaluated the safety and efficacy of casirivimab and imdevimab. This trial was undertaken to gain an understanding of the natural history of Covid-19 in outpatients, and to refine the end points for subsequent analyses. 275 patients were randomly assigned (1:1:1) to receive placebo, REGN-COV2 at a dose of 2.4 g (low dose), or REGN-COV2 at a dose of 8.0 g (high dose). The authors reported that casirivimab with imdevimab reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Safety outcomes were similar in the combined REGN-COV2 dose groups and the placebo group. The specifc variant of prevalent SARS-CoV-2 was not recorded.

1.11.2. 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 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 COVID19-related hospitalization or all-cause death compared to placebo (2.4 gm: 71.3% reduction [1.3% vs 4.6%; p<0.0001] calculated NNT - 30 and 1.2 gm: 70.4% reduction [1.0% vs 3.2%; p=0.0024], calculated 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. Details of the variant of SARS-CoV-2 was not available. 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).

1.12. The Advisory Group considered that the NNT of 30-45 for preventing progression to hospitalisation or death for patients with mild to moderate COVID-19 in the community was relatively high. The Advisory Group considered that the NNT could be reduced by targeting treatment to those people particularly at risk of developing severe COVID-19.

1.13. The Advisory Group noted that the trials for casirivimab and imdevimab in the treatment of COVID-19 had been undertaken prior to mass vaccination. The Advisory Group considered that in the future as New Zealand's population becomes increasingly vaccinated, cases of COVID-19 are likely to occur in vaccinated individuals. On balance The Advisory Group considered that patients who are seronegative at the time of treatment appear to receive the greatest benefit from treatment with casirivimab and imdevimab. Noting the limited availability of stock, the Advisory Group considered that treatment with casirivimab and imdevimab should be restricted to patients who have not been vaccinated against COVID-19, are seronegative at the time of treatment, or unlikely to have been able to mount an immune response due to immune suppression.

The Advisory Group noted that New Zealand data indicates that Māori are overrepresented in terms of COVID-19 incidence and hospitalisation in New Zealand. Members noted that, from the data available at the time of the 13 December 2021 meeting, Māori people accounted for 45% of cases and 34% of hospitalisations and Pacific peoples accounted for 29% of cases and 38% of hospitalisations. In contrast New Zealand European and Asian people accounted for 19% and 6% of cases respectively and 21% and 2% of hospitalisations respectively. Members noted that despite higher case numbers than other ethnic groups Māori were hospitalised at proportionately lower rates than other ethnic groups (4% compared for Māori compared to 6.1% for New Zealand European). Members considered that this may be explained by the barriers faced by Māori people in accessing healthcare in New Zealand, rather than suggesting less severe illness in this group. Based on this information the Advisory Group considered that Māori and Pacific ethnicity should be considered as a risk factor for severe disease in New Zealand.

1.14. The Advisory Group noted that the trials for casirivimab and imdevimab in treatment of COVID-19 that had been considered at the Advisory Groups' October 2021 meeting used different age cut-offs to indicate risk of severe COVID-19. The Advisory Group considered that an age of 50 years and above would be an appropriate age cut off for risk of severe COVID-19 infection in New Zealand.

1.15. The Advisory Group considered it would be reasonable to assume that the greater number of risk factors a patient has the greater their risk of progressing to severe COVID-19. The Advisory Group considered that ≥3 risk factors for developing severe COVID-19 would be appropriate for access casirivimab and imdevimab in the community. The number of risk factors for developing severe COVID-19 used to determine access criteria for Casirivimab/imdevimab was partly dependant on the available supply of Casirivimab/imdevimab.

1.16. The Advisory Group noted that there was emerging evidence, which indicated that while casirivimab imdevimab was effective against the Delta Variant of COVID-19 it did not appear to be effective against the Omicron variant of COVID-19. The Advisory Group considered that based on available information it was likely that the Omicron variant of COVID-19 would become the dominant strain of COVID-19 in New Zealand and globally.

1.16.1. The Advisory Group considered that it was important that casirivimab and imdevimab was used in the treatment of the Delta Variant of COVID-19 to ensure it is not wasted. The Advisory Group considered it would be preferable to widen access to casirivimab and imdevimab to include groups in the community at risk of severe COVID-19 while the Delta Variant of COVID-19 remained in circulation. The Advisory Group noted that stock that is not able to

be used in the treatment of the Delta Variant of COVID-19 could be stored for future use in the event that it is effective against future strains of COVID-19.

1.16.2. The Advisory 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.

1.17. The Advisory Group noted that oral antivirals were expected to be available in New Zealand for the treatment of COVID-19 in the first half of 2022, and considered it was likely that these treatments would be easier to use in the community. The Advisory Group considered that oral antivirals would offer a suitability benefit for the majority of patients in the community with COVID-19 as they are able to be taken orally rather than requiring an IV infusion or subcutaneous injection; however, the Advisory Group acknowledged that casirivimab and imdevimab was expected to be available in New Zealand before oral antiviral treatments. Consequently, the Advisory Group considered that it would be beneficial for clinicians and patients to have access to casirivimab and imdevimab in for the treatment of COVID-19 in the community prior to the availability of oral antiviral treatments.

1.18. The Advisory Group noted that the best defence against COVID-19 continues to be vaccination and considered that it is important that any funding of COVID-19 treatments do not undermine New Zealand's vaccination efforts.

2. Regdanvimab

Application

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

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

Recommendation

2.3. The Advisory Group noted that the supplier had sought funding of regdanvimab for adults with mild to moderate COVID-19 symptoms who do not require hospitalisation and are at high risk of progressing to severe disease.

2.4. The Advisory Group **recommended** that regdanvimab not be funded for the treatment of COVID-19 at this time, on the basis of the limited volume and low-quality strength of evidence available for regdanvimab in this setting.

2.5. In making this recommendation the Advisory Group acknowledged the importance of securing a portfolio of treatments for COVID-19 for New Zealand and noted it would welcome any additional information the supplier is able to provide about the effectiveness of regdanvimab in the treatment of COVID-19.

2.6. The Advisory Group agreed that for it to reconsider regdanvimab for the treatment of COVID-19 the following information would be particularly useful

2.6.1. Peer reviewed and published trial data demonstrating the effectiveness of regdanvimab in the treatment of COVID-19;

2.6.2. Evidence demonstrating the effectiveness of reganvimab in the treatment of people with COVID-19 variants of concern including Omicron and Delta.

2.7. 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.

2.8. 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.

Discussion

2.9. The Advisory Group noted that regdanvimab is a monoclonal antibody that binds to the SARS-CoV-2 spike protein. Binding to the spike protein prevents the virus from binding to the ACE receptor, thereby blocking virus entry into cells.

2.10. The Advisory Group noted that unlike other monoclonal antibodies, developed for the treatment of COVID-19, such as casirivimab and imdevimab and tixagevimab and cilgavimab which are combinations of two monoclonal antibodies and bind to different sites on the spike protein, regdanvimab is a single monoclonal antibody. The Advisory Group considered there was uncertainty regarding the impact of this on the effectiveness of regdanvimab, against COVID-19 variants of concern.

2.11. The Advisory Group noted that the recommended dose of regdanvimab in adults is a single intravenous infusion of 40 mg/kg administered over 90 minutes. Regdanvimab should be administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

2.12. The Advisory Group noted that regdanvimab is being investigated for the treatment of COVID-19 in outpatients who do not require supplemental oxygen.

2.13. The Advisory Group considered the following clinical evidence for regdanvimab for the treatment of COVID-19:

2.13.1. Outpatients with mild to moderate COVID-19: Eon, Ison, Streinu-Cercel, et al, 2021

Part 1 of study 3.2, was a phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study evaluating the efficacy, safety, pharmacokinetics and virology of regdanvimab in outpatients with mild to moderate COVID-19,. Participants aged 18 or above, diagnosed with SARS-CoV-2 infection with oxygen saturation >94% on room air and not requiring supplemental oxygen with symptom onset no more than 7 days prior to the regdanvimab administration were randomly assigned to receive regdanvimab 40 mg/kg, 80 mg/kg or placebo. Clinical symptoms requiring hospitalization, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection was lower in the regdanvimab group compared to the placebo group (4[4%], 5[4.9%], 9[8.7%] patients in the regdanvimab 40mg/kg, 80mg/kg, and placebo group respectively).

2.13.2. Outpatients with mild to moderate COVID-19 at risk of progressing to severe disease

Part 2 of study 3.2, was a phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study evaluating the efficacy, safety and virology of regdanvimab in outpatients with mild to moderate COVID-19. Participants aged 18 or above, diagnosed with SARS-CoV-2 infection with oxygen saturation >94% on room air and not requiring supplemental oxygen with symptom onset no more than 7 days prior to the regdanvimab administration were randomly assigned to receive regdanvimab 40 mg/kg, or placebo. The primary objective was to demonstrate clinically meaningful therapeutic efficacy of regdanvimab by the proportion of patients with clinical symptoms requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high-risk patients. Results showed that for high risk patients the risk of disease progression (requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection) through Day 28, was 72% lower for patients treated with regdanvimab (40 mg/kg) compared to the placebo group (14 [3.1%] and 48 [11.1%] patients in the regdanvimab 40 mg/kg and placebo groups, respectively), ($p<0.0001$). For all randomised patients treated with regdanvimab 40 mg/kg results showed a 70% reduction in the risk of disease progression through Day 28 compared to Placebo (16 [2.4%] and 53 [8.0%] patients in the regdanvimab 40 mg/kg and Placebo groups, respectively), ($p<0.0001$).

2.13.2.1. The Advisory Group noted that Part 1 of study 3.2 was a preprint of an interim analysis of a randomised controlled trial (RCT), which had not undergone peer review and was not published.

2.13.2.2. The Advisory Group noted in Part 1 of study 3.2 COVID-19–related hospitalisation, oxygen therapy or death occurred in four and five patients for the regdanvimab 40mg/kg and 80mg/kg groups respectively compared to 9 patients in the placebo group. The Advisory Group considered that based on these small patient numbers it was difficult to draw conclusions about the efficacy of regdanvimab in this setting.

2.13.2.3. The Advisory Group noted that Part 2 of study 3.2 was not yet published; however, information regarding this study had been provided by the supplier in documentation provided to the European Medicines Agency to support its review of regdanvimab.

2.13.2.4. The Advisory Group considered that there was uncertainty regarding how similar the trial population in study 3.2 was to the current New Zealand population with COVID-19, noting that the trial was completed in 2020, prior to the availability of COVID-19 vaccinations, oral antiviral treatments and the Delta and Omicron variants of COVID-19.

2.13.2.5. The Advisory Group considered that study 3.2 used more liberal criteria for patients considered to be high risk of progressing to severe COVID-19, than the criteria used by the Ministry of Health, including age of 50 years or more, Body Mass Index BMI of more than 30 kg/m^2, cardiovascular disease, including hypertension, chronic lung disease, including asthma, Type 1 or type 2 diabetes mellitus, chronic kidney disease, including those on dialysis, chronic liver disease and immunosuppressed people. The Advisory Group noted that it was not known what proportion of higher risk patients as defined by study 3.2

would also meet the Ministry of Health's criteria for a patient to be defined as high risk of progressing to severe COVID-19, and to what extent the outcomes of death or hospitalisation in study 3.2 was confined to this higher risk group.

2.13.2.6. On balance the Advisory Group considered that it was likely that patients at greater risk of severe COVID-19 would benefit more from treatment with regdanvimab than other patient groups. .

2.13.3. Patients hospitalised with confirmed mild to moderate COVID-19: Jang, Oh and Kim, 2021

A phase 3 retrospective cohort study evaluating the effectiveness of regdanvimab in patients hospitalised with mild to moderate COVID-19. Results showed that the proportion of patients who deteriorated with SpO2 <94% in room air or received remdesivir up to Day 28 was 15.0% with regdanvimab and 45.8% with SoC (p<0.0001); median time (range) until sustained recovery of fever was 2.0 (0.2–14.8) and 4.2 (0.1–17.1) days, respectively. Supplemental oxygen was required by 23.6% of patients with regdanvimab and 52.1% with SoC (p<0.0001) for a mean duration of 6.3 and 8.7 days, respectively (p=0.0113); no patients needed mechanical ventilation.

2.13.4. The Advisory Group considered that the results indicated by the study end points (for example treatment with remdesivir, deterioration with SpO2 <94%, the requirement for supplemental oxygen) were unclear and did not necessarily indicate the effectiveness of regdanvimab in the treatment of COVID-19.

2.13.5. The Advisory Group considered the retrospective nature of the study design meant that the reported results were likely subject to a number of confounding risks, which may impact the validity of the reported results for regdanvimab in the treatment of COVID-19.

2.13.6. Adults confirmed as negative for SARS-CoV- 2 infection: Study 1.1

A phase 1 randomized, double-blind, placebo-controlled, parallel-group, single ascending dose study to evaluate the safety, tolerability and pharmacokinetics of regdanvimab in healthy subjects. The primary objective was to evaluate the preliminary safety and tolerability of regdanvimab up to Day 14 of the last enrolled subject. The secondary objective was to evaluate the pharmacokinetics of regdanvimab, as well as the additional safety and immunogenicity of regdanvimab. Results showed that Single IV infusion over 90 minutes (±15 minutes) of regdanvimab in doses of 10 mg/kg, 20 mg/kg, 40 mg/kg and 80 mg/kg was safe and well-tolerated in healthy subjects and no new major safety concerns.

2.13.7. Adults with laboratory confirmed SARS-CoV- 2 infection, with mild symptoms: Study 1.2

A randomized, double-blind, placebo-controlled, parallel group, single ascending dose, Phase 1, pilot study to evaluate the safety, tolerability and virology of regdanvimab in combination with standard of care (SoC) in patients with mild symptoms of SARS-CoV-2 infection. The primary objective was to evaluate the preliminary safety and tolerability of regdanvimab up to Day 14 of the last enrolled patient. The secondary objective of this study was to evaluate the viral efficacy and characterization of SARS-CoV-2 viral isolates, efficacy,

Pharmacokinetics and additional safety of regdanvimab including immunogenicity. Results showed that Single IV infusions of regdanvimab in doses of 20 mg/kg, 40 mg/kg and 80 mg/kg proved to be safe and well-tolerated in patients with mild SARS-CoV-2 infection up to Day 14. In general, patients with max viral titre over 5 log10cp/mL based on qPCR had greater reductions in viral shedding up to Day 7 after receiving regdanvimab than placebo.

2.13.8. Effectiveness against variants of concern Ryu, Kang and Noh et al 2021

2.13.8.1. The Advisory Group considered a study by Ryu, Kang and Noh et al which used cell tests and animal studies to evaluate the effectiveness of regdanvimab against COVID-19 variants of concern. The Advisory Group noted an animal study in which mice were administered doses of 5, 20, 40 and 80 mg/kg of regdanvimab was used to evaluate the in vivo potency of regdanvimab against the Gamma and Delta variants of COVID-19 and a microneutralization assays were used to evaluate the in vitro potency of regdanvimab against the Gamma, Delta, Epsilon, and Kappa variants of COVID-19. Results demonstrated that regdanvimab retained neutralisation effect against the Gamma, Delta, Epsilon, and Kappa variants of COVID-19; however, this was reduced compared to the neutralisation effect of regdanvimab against wild type SARS-CoV-2.

2.13.8.2. The Advisory Group noted that the neutralisation effect of regdanvimab was approximately 100-fold and 183-fold less effective against pseudovirus and live virus of the Delta Variant of COVID-19 compared to wild type COVID-19.

2.13.8.3. The Advisory Group noted that mice treated with 5 mg/kg and 20 mg/kg of regdanvimab showed a delay in weight loss associated with SARS-CoV-2 infection until 6 days post infection; however, only treatment with 40 mg/kg and 80mg/kg of regdanvimab showed a statistically significance difference in weight loss compared to placebo at 4 days and five days post SARS-CoV-2- infection.

2.14. The Advisory 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 Advisory 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.

2.15. The Advisory Group noted that there was limited evidence for regdanvimab in the treatment of the Delta Variant of COVID-19 and there was no evidence for regdanvimab in the treatment of Omicron Variant of COVID-19. The Advisory Group considered it was expected that Omicron would become the dominant variant of COVID-19 globally and in New Zealand and considered it would be important to review evidence regarding the effectiveness of regdanvimab against the Omicron variant of COVID-19 before any funding recommendations could be made.

2.16. The Advisory Group noted there was no evidence for regdanvimab for prophylaxis post exposure to COVID-19 or the treatment of severe COVID-19. In addition,

there were no studies of the effectiveness of regdanvimab in the treatment of COVID-19 in population sub groups such as vaccinated individuals, pregnant people or children.

2.17. Overall, The Advisory Group considered that the strength of evidence supporting the use of regdanvimab in the treatment of patients with mild to moderate COVID-19 in both outpatient and hospital settings was good; however, the quality of the available evidence was poor.

2.18. The Advisory Group noted that regdanvimab has been approved for use in Korea and the European Medicines Agency has adopted a positive scientific opinion, recommending the granting of a marketing authorisation for regdanvimab for the treatment of adults with COVID-19.

2.19. The Advisory Group noted that the Therapeutic Goods Administration (TGA) has granted provisional determination to the supplier for regdanvimab in Australia; however, the Australian Guidelines for the clinical care of people with COVID-19 did not recommend the use of regdanvimab for the treatment of COVID-19 outside randomised trials.

2.20. The Advisory Group discussed that regdanvimab was required to be administered via IV infusion. The Advisory Group considered that administering regdanvimab via infusion 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.

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

2.22. The Advisory Group noted that New Zealand data indicates that Māori are overrepresented in terms of COVID-19 incidence and hospitalisation. Members noted that, based on data available at the time of the 13 December 2021 meeting, Māori people accounted for 45% of cases and 34% of hospitalisations and Pacific peoples accounted for 29% of cases and 38% of hospitalisations. In contrast New Zealand European and Asian people accounted for 19% and 6% of cases respectively and 21% and 2% of hospitalisations respectively.

2.23. The Advisory Group considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for regdanvimab 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 Advisory 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 regdanvimab if it were to be funded in New Zealand for mild to moderate COVID-19.

Population	• Adults with mild to moderate COVID-19 symptoms with oxygen saturation >94% in room air who do not require hospitalisation and are at high risk of progressing to severe disease within 7 days of symptom onset.

	• Immunocompromised or unvaccinated people with COVID-19 at risk of progressing to severe disease. • Other monoclonal antibodies with greater proven efficacy are not available
Intervention	40mg/kg intravenous infusion
Comparator(s) (NZ context)	Standard of care Casirivimab and imdevimab Oral antiviral treatments
Outcome(s)	Reduced hospitalisations Reduced time to recovery
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.	

2.24. The Advisory Group considered there was significant uncertainty regarding the number of people in New Zealand who may become infected with SARS-CoV-2 and require treatment with monoclonal antibodies such as regdanvimab. The Advisory Group noted Te Pūnaha Matatini (TPM) modelling detailing possible maximum numbers of COVID-19 cases in New Zealand 2022 and international data provided by Pharmac staff; however, The Advisory Group considered that international modelling did not reflect the New Zealand population and COVID-19 response. In addition, The Advisory Group noted the majority of available COVID-19 modelling was undertaken prior to the detection of the Omicron variant of COVID-19 and consequently was unlikely to reflect possible COVID-19 case numbers in New Zealand in 2022.

Tixagevimab and cilgavimab for the treatment and prophylaxis of COVID-19

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

Recommendation

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

Restricted
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. Patient is >12 years of age, and at risk of inadequate immune response to SARS-CoV-2 vaccination or infection as described by eligibility criteria for a third primary COVID-19 dose by Ministry of Health*
2. Patient does not currently have SARS-CoV-2 infection

Note: *Third Primary dose eligibility criteria as defined on Ministry of Health Website

Restricted
Indication – 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 not completed course of vaccination** OR is at risk of inadequate immune response to SARS-CoV-2 vaccination as described by eligibility criteria for a third primary COVID-19 vaccine dose by Ministry of Health. ***
2. Patient has confirmed (or probable) symptomatic COVID-19; and
3. Patient is ≤7 days of symptom onset; and
4. Patient is at risk of developing severe illness****; and
5. Either;
   5.1. Patient does not require supplemental oxygen (to maintain oxygen saturation >93%); or
   5.2. Patient does not require supplemental oxygen to maintain oxygen saturations no lower than baseline (for patients with chronic resting hypoxia); and
6. Dominant circulating SARS-CoV-2 variant is anticipated to be susceptible to neutralisation by tixagevimab/cilgavimab

Note:
*Mild to moderate disease severity as described on the Ministry of Health Website.
**Fully Vaccinated' defined as per the Ministry of Health definition
***Third Primary dose eligibility criteria as defined on Ministry of Health Website.
**** People with high-risk medical conditions identified by the Ministry of Health

3.3. The Advisory Group noted that tixagevimab and cilgavimab were fully human monoclonal antibodies originally derived from the B-cells of patients who had recovered from COVID-19. The monoclonal antibodies were then modified (at the Fc region) to increase longevity after administration. Tixagevimab and cilgavimab simultaneously bind two sites of the SARS-CoV-2 Receptor Binding Domain (RBD). This interrupts binding of the SARS-CoV-2 spike protein to angiotensin-converting enzyme 2 (ACE2) receptors present on human cells, which is the primary mechanism of cellular entry used by SARS-CoV-2..

3.4. The Advisory Group noted that tixagevimab and cilgavimab is undergoing trials for multiple indications related to COVID-19, specifically for pre-exposure prophylaxis, post-exposure prophylaxis, outpatient treatment and inpatient treatment.

Pre-exposure prophylaxis against COVID-19 infection:

3.5. The Advisory Group considered the number of patients who would benefit from the use of tixagevimab and cilgavimab for pre-exposure prophylaxis was difficult to estimate, but considered that the appropriate group would be those who would be at risk of severe COVID-19 disease because they may have limited response to a vaccination series.

3.6. The Advisory Group considered the evidence of Kearns, P et al., Tenforde MW, Self WH, Naioti EA, et al. and Embi, P. J. et al with regard to defining groups which are unlikely to respond to COVID-19 vaccination. The Advisory Group considered that while proportion of vaccine response in immunocompromised groups is variable, and sometimes profoundly reduced after a second dose, the evidence demonstrated that a third dose of Pfizer-BioNTech vaccine increased the proportion of those with a measurable immune response by a further 30-50%.

3.7. The Advisory Group considered the Ministry of Health's guidance on people eligible for a third dose of a COVID-19 vaccination to inform the size of The

Advisory Group who would benefit from tixagevimab and cilgavimab prophylaxis. This group included people with primary or acquired immunodeficiency, chronic inflammatory/autoimmune disease, current/recent immunosuppressive therapy and long-term renal replacement therapy.

3.8. The Advisory Group considered evidence provided by the supplier about the size of the potential at risk group. The Advisory Group noted that depending on the criteria used these estimates range from 20,000 to 70,000 people in New Zealand.

3.9. The Advisory Group considered that in the current New Zealand context, the number needed to treat to prevent one hospitalisation or death was hard to calculate but likely to be high. In this setting, medication adverse effects such as an observed increased rate of cardiac events in trial participants with pre-existing cardiac risk factors could mean that the number needed to harm is lower than the number needed to treat. Caution should be used in recommending tixagevimab and cilgavimab when there is a low prevalence of hospitalisation and death from COVID-19 in the community, particularly for people with pre-existing cardiac risk factors who may be at greater risk of harm.

Treatment of mild-moderate COVID-19 infection:

3.10. The Advisory Group noted the similarity to casirivimab & imdevimab and other monoclonal antibody treatments and the data provided by the supplier on the TACKLE trial. The Advisory Group noted that the eligibility criteria should be similar to casirivimab & imdevimab and that early administration appeared to be an important factor to the effectiveness of the treatment.

3.11. The Advisory Group considered the unique differentiators of tixagevimab and cilgavimab compared to other available and potential treatments for COVID-19 as its intramuscular injection method of administration and its long lasting effects.

3.12. The Advisory Group noted that Pharmac has estimated that 24% of symptomatic cases would be deemed as 'high risk' (as per the MoH definition) using an age proxy (all cases over the age of 60 years) due to the similarities in cases/hospitalisation observed. Members considered that this was likely an underestimate and that the high-risk group would be a larger proportion.

3.13. The Advisory Group noted that based on November 2021 data, Māori and Pacific peoples accounted for 74% of all COVID-19 cases in the outbreak beginning August 2021, which is a higher proportion than seen in 2020 (Ministry of Health. December 2021). The Advisory Group considered that this further demonstrates that Māori and Pacific ethnicity is a risk factor for developing symptomatic COVID-19 infection. The Advisory Group noted that while case numbers were higher for Māori and Pacific than other ethnic groups, hospitalisations rates were also disproportionately higher. Members discussed that this data and resulting variation is influenced by many confounders and may be explained by disparities such as barriers to access hospital services, as well as unconscious bias within the health system. The Advisory Group noted that currently the Ministry of Health's guidance on risk factors for individuals at higher risk of the effects of COVID-19 infection includes Māori and Pacific ethnicity (Ministry of Health. December 2021).

3.14. The Advisory Group noted that the single dose, long lasting effects of tixagevimab and cilgavimab could be an advantage when treating underserved populations such as Māori and Pacific peoples.

3.15. The Advisory Group considered that while the Ministry of Health's guidance does include ethnicity as a risk factor, it was important to include Māori and Pacific ethnicity as a specific criterion in Special Authority to remove any unnecessary and/or biased access barriers and to also allow for evaluation of equitable treatment uptake. The Advisory Group noted that at present tixagevimab and cilgavimab was the only non-vaccine option for pre-exposure prophylaxis and that its efficacy does not depend upon the immune system of the patient. The Advisory Group considered the possibility of vaccine interactions (i.e. reduced efficacy of vaccination after receiving tixagevimab and cilgavimab) and noted that this was uncertain but that could be followed up with the Immunisation Specialist Advisory Committee and/or The Ministry of Health's COVID-19 Vaccine Technical Advisory Group. The Advisory Group considered that from the clinical data it was unclear when in the course of a vaccine series tixagevimab and cilgavimab should be given for greatest effect.

3.16. The Advisory Group recommended that communications around the potential availability of tixagevimab and cilgavimab be carefully considered as to avoid interfering with the COVID-19 vaccination program. The Advisory Group noted that tixagevimab and cilgavimab is inferior to and should not be positioned as an alternative to vaccination for immunocompetent people.

3.17. The Advisory Group considered the safety profile of tixagevimab and cilgavimab based on clinical data provided by the supplier. The Advisory Group noted that generally the treatment was safe and well tolerated but that there was a possible signal for cardiovascular risk noted by FDA EUA and a potential risk of haematoma after IM injection inpatients receiving anticoagulation or with disordered coagulation (e.g. severe thrombocytopenia). The Advisory Group also noted the FDA EUA for pre-exposure prophylaxis aligned with the US CDC's definition of "moderate or severe immunocompromise" which was narrower than the New Zealand Ministry of Health's third primary COVID-19 vaccine dose groups. due to exclusion of kidney dialysis patients or those with untreated malignancies.

3.18. The Advisory Group considered the intramuscular method of administration compared favourably in terms of suitability to similar monoclonal antibody treatments which required intravenous infusion.

3.19. The Advisory Group considered the use of SARS-CoV-2 serostatus as a marker for identifying people who would benefit from tixagevimab and cilgavimab. The Advisory Group considered that there are many challenges with large scale testing of serostatus and that there are no standardised levels or thresholds of protection. The Advisory Group noted that the US CDC does not recommend antibody testing as a means of assessing response to vaccination and the UK Green book recommended only when requested by specialists for immunocompromised patients.

3.20. The Advisory Group noted serostatus as a marker for tixagevimab and cilgavimab use required further investigation and discussion with the New Zealand laboratory network.

3.21. The Advisory Group considered the efficacy of tixagevimab and cilgavimab for pre-exposure prophylaxis to be moderate from the clinical evidence provided and the quality of clinical evidence was strong but limited. The evidence for early treatment was felt to be weak, with low-moderate quality due to limited evidence available at time of discussion. The Advisory Group noted that the treatment of

very high-risk people prophylactically was likely to provide the greatest benefit but that the number needed to treat (NNT) metric was difficult to calculate due to a large number of potential confounding factors and the ongoing generation of new Variants of Concern (VoC) of the SARS-COV-2 virus.

3.22. The Advisory Group considered that as a monoclonal antibody therapy tixagevimab and cilgavimab is likely to be vulnerable to novel SARS-CoV-2 Variants of Concern (VoC). The Advisory Group considered the ability of tixagevimab and cilgavimab to neutralise the Delta VoC in Loo YM et al as likely to support efficacy against the Delta VoC.

3.23. The Advisory Group noted the rapid spread of the Omicron VoC and the potential for it to both outcompete the currently dominant Delta VoC and evade current treatments. The Advisory Group considered Xiaoliang Xie, Yunlong Cao, Jing wang et al. which showed potential for reduced efficacy of many monoclonal antibody treatments against the Omicron VoC.

Population	Prophylaxis of COVID-19 disease in groups at risk of inadequate immune response to SARS-CoV-2 vaccination or infection
Intervention	Tixagevimab and cilgavimab 300mg (two intramuscular doses administered sequentially)
Comparator(s) (NZ context)	Best standard of care PfizerBioNT Comirnaty vaccine (2/3 doses)
Outcome(s)	Reduced hospitalisations Reduced infection rates

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.

Population	Treatment of mild-moderate COVID-19 disease (≤5 days from symptom onset) in groups at risk of progression to severe disease
Intervention	Tixagevimab and cilgavimab 600mg (two intramuscular doses administered sequentially)
Comparator(s) (NZ context)	Best standard of care Antiviral treatments for COVID-19 Casirivimab & imdevimab
Outcome(s)	Reduced mortality Reduced hospitalisations Reduced infection rates Reduced hospital stay duration Improved time to recovery

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.

Remdesivir for the treatment of COVID-19

Application

4.1. The Advisory Group reviewed material provided by Pharmac staff regarding the use of remdesivir for the treatment of COVID-19.

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

4.3. The Advisory Group noted that remdesivir is a direct-acting nucleotide prodrug inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase, which is required for viral replication.

Recommendation

4.4. The Advisory Group recommended that remdesivir 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 access criteria:

Initial Application – (Acute COVID-19 disease) Any relevant practitioner. Approvals valid for a 3 day treatment course for all applications meeting the following criteria: All of the following:

1 Patient has confirmed (or probable) symptomatic COVID-19; and
2 Patient is ≤7 days of symptom onset: and
3Either:
- 3.1 Patient is at risk of developing severe illness*; or
- 3.2 Patient is Māori or any Pacific ethnicity; and

5 Patient does not require supplemental oxygen (oxygen saturation >93%)**; and
6 Not to be used in conjunction with other COVID-19 antiviral treatments

*Note: Patients at risk of severe illness from COVID-19, excluding pregnancy, as described on the Ministry of Health website

**or saturations no lower than baseline for patients with chronic resting hypoxia

Restricted
Initiation – mild to moderate COVID-19-hospitalised patients
Limited to 5 days
All of the following:
1. Patient has confirmed (or probable) COVID-19; and
2. Patient is an in-patient in hospital with acute COVID-19 disease ; and
3. Patient is ≤10 days of symptom onset ; and
4. Either:
    4.1 Patient is at risk of developing severe illness*; or
    4.2 Patient is Māori or any Pacific ethnicity; and
5. Patient is not receiving high flow oxygen or assisted/mechanical ventilation; and
6. Not to be used in conjunction with other COVID-19 antiviral treatments

*Note: Patients at risk of severe illness from COVID-19, excluding pregnancy, as described on the Ministry of Health website

4.5. The Advisory Group noted that the proposed criteria were informed by the PINETREE study, which is not yet published. The Advisory Group considered that amendments may need to be made to the recommended criteria following publication.

4.6. Members noted remdesivir does not currently have regulatory approval for use in New Zealand; however, an application is currently under review by Medsafe.

4.7. 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 it did not need to discuss a priority ranking.

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

Discussion

4.9. The Advisory Group noted that remdesivir is currently available in New Zealand and is funded for the treatment of patients hospitalised with COVID-19

4.10. The Advisory Group noted that the access criteria for remdesivir had been previously considered by Pharmac's Ad Hoc Remdesivir COVID-19 Advisory Group which recommended remdesivir be funded in line with the criteria for access to remdesivir from the Australian National Medical Stockpile.

4.11. The Advisory Group noted that since remdesivir was first considered by the Ad Hoc Remdesivir COVID-19 Advisory Group in September 2020, evidence for its use in the treatment of COVID-19 has continued to emerge. The Advisory Group considered it was timely to consider the latest evidence for the use of remdesivir for the treatment of COVID-19.

4.12. The Advisory Group considered that the health need of those with COVID-19 is high for the individual, their whānau, the wider community.

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

4.14. The Advisory Group considered clinical evidence for remdesivir for the treatment of COVID-19.

4.15. Ansems et al. Cochrane Database Syst Rev. 2021;8(8).

A Cochrane living systematic review to assess the effects of remdesivir compared to placebo or standard care alone in hospitalised patients with SARS-CoV-2 infection. The authors concluded that for adults hospitalised with COVID-19, remdesivir probably has little or no effect on deaths from any cause up to 28 days after treatment compared with placebo or standard care. In addition, the authors concluded that remdesivir may have little or no effect of the length of time a patient spends on mechanical ventilation or supplemental oxygen.

4.15.1. The Advisory Group noted that the review assessed the effects of remdesivir in patients hospitalised with SARS-CoV-2 infection and did not include patients in outpatient settings with mild to moderate COVID-19 infection.

4.16. Gottlieb, et al. N Engl J Med. 2021; NEJMoa2116846

An ongoing randomized, double-blind, placebo-controlled trial (PINETREE study) involving non-hospitalised patients with COVID-19 who had symptom onset with in the previous 7 days and who had at least one risk factor for disease progression (age ≥ 60 years, obesity, or certain coexisting medical conditions). Patients were randomly assigned to receive intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) or placebo. The primary efficacy end point was a composite of Covid-19–related hospitalization or death from any cause by day 28. The primary safety end point was any adverse event. A secondary end point was a composite of a Covid-19–related medically attended visit or death from any cause by day 28. A total of 562 patients who underwent randomization and received at least one dose of remdesivir or placebo were included in the analyses: 279 patients in the remdesivir group and 283 in the placebo group. Covid-19–related hospitalization or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.03 to 0.59; P=0.008). A total of 4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group had a Covid-19–related medically attended visit by day 28 (hazard ratio, 0.19; 95% CI, 0.07 to 0.56). No patients had died by day 28. Adverse events occurred in 42.3% of the patients in the remdesivir group and in 46.3% of those in the placebo group.

4.16.1. The Advisory Group noted that the number needed to treat (NNT) to prevent one hospitalisation or death in this population would be approximately 13, which was lower than other treatments recommended by The Advisory Group for funding for the treatment of mild to moderate COVID-19.

4.16.2. The Advisory Group noted that at the time of the 13 December 2021 Advisory Group meeting the PINETREE study results were unpublished and had not yet undergone peer review.

4.16.3. The Advisory Group noted that there was limited information available on the trial participants, which may impact the recommendations made by The Advisory Group once this information is available.

4.16.4. The Advisory Group considered that if the peer reviewed publication of the PINETREE study demonstrated similar efficacy as the unpublished results for the treatment of mild to moderate COVID-19, remdesivir may be a suitable alternative to other antiviral treatments and monoclonal antibodies that are currently recommended for the treatment of mild to moderate COVID-19.

4.17. Based on the available evidence The Advisory Group considered that remdesivir is likely to offer the most benefit to patients in the early stages of COVID-19 infection (≤ 10 days of symptom onset), prior to hospitalisation with risk factors of progressing to severe disease, including profoundly immunocompromised people. The Advisory Group considered remdesivir is likely to offer little to no benefit to patients hospitalised with moderate to severe COVID-19 infection; however, there may be a small group of patients hospitalised with more mild COVID-19 (requiring supplemental oxygen but not ventilated) who are ≤ 10 days from the onset of symptoms, who may benefit from treatment with remdesivir in terms of a reduced likelihood of disease progression and/or death.

4.18. The Advisory Group considered the treatment paradigm for COVID-19 and noted that the use of remdesivir early in the treatment of COVID-19 would require a change in clinical practice in New Zealand as remdesivir is currently used in the treatment of patients once they become hospitalised with COVID-19.

4.19. The Advisory Group noted that the benefit associated with remdesivir appeared to be associated with administration as early as possible following symptom onset rather than the severity of disease being treated

4.20. The Advisory Group noted that remdesivir was required to be administered via IV infusion. The Advisory Group considered that administering remdesivir via IV infusion in the community would be resource intensive and the resource and infrastructure required to deliver this, particularly in rural communities has not been established and may be limited in some areas of New Zealand.

4.21. The Advisory Group noted that remdesivir is not approved by Medsafe and therefore needs to be prescribed in accordance with Section 25 and supplied under Section 29 of the Medicines Act 1981. The Advisory Group considered that the unapproved status of remdesivir could raise barriers for access to this treatment in the community due to additional reporting requirements for clinicians and patient acceptance of an unapproved treatment.

4.22. The Advisory Group acknowledged there were a number of drawbacks associated with the use of remdesivir in the community and that, orally administered antiviral treatments for COVID-19, expected to be available in 2022 such as nirmatrelvir with ritonavir, and molnupiravir would offer suitability benefits compared to remdesivir in community settings; however, The Advisory Group noted that remdesivir is the only antiviral treatment for COVID-19 currently available in New Zealand. The Advisory Group considered that in light of the continuing spread of COVID-19 and the possibility of an omicron outbreak in New Zealand it may be preferable to have remdesivir available for use in the community until more suitable treatments are available.

4.23. The Advisory Group considered that following the availability of oral antiviral treatments in New Zealand, such as molnupiravir and nirmatrelvir with ritonavir, use of remdesivir is likely to reduce; however, it may continue to be appropriate for a small group of patients in the community for whom oral antivirals are not appropriate.

4.24. The Advisory Group noted that within 6 months it is likely that the majority of New Zealand's COVID-19 would occur in vaccinated people and considered that remdesivir could have a role in the treatment of breakthrough COVID-19 infection.

4.25. The Advisory Group noted that Māori and Pacific peoples are disproportionality affected by COVID-19 in New Zealand; ~45% of current COVID-19 cases are Māori and 39% of all hospitalised cases are Māori. ~29% of current cases are Pacific peoples and ~34% of hospitalised cases are Pacific peoples.

4.26. The Advisory 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 and treatment. Consequently, The Advisory Group considered that availability of remdesivir in the community would be particularly beneficial for Māori and Pacific peoples relative to other ethnic groups in New Zealand.

4.27. The Advisory Group considered that it was important that if remdesivir was to be funded for a wider range of patients with COVID-19 that it did not negatively impact the Government's COVID-19 vaccination programme through the perception of being an alternative to vaccination.

Pfizer's oral protease inhibitor (nirmatrelvir with ritonavir) for mild to moderate COVID-19

Application

5.1. The Advisory Group reviewed the available evidence (as at 13 December 2021) regarding the use of Pfizer's oral protease inhibitor (nirmatrelvir with ritonavir) for the treatment of mild to moderate COVID-19.

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

Recommendation

5.3. The Committee recommended that nirmatrelvir with ritonavir be funded subject to the following Special Authority / Hospital Restriction criteria.

Initial Application – (Acute COVID-19 disease) 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 Either:
    3.1 Patient is at risk of developing severe illness*; or
    3.2 Patient is Māori or any Pacific ethnicity; and
4 Patient does not require supplemental oxygen (oxygen saturation >93%)**; and
5 Either:
    5.1 Patient has not completed the full primary vaccination schedule for COVID-19; or
    5.2 Patient is immune compromised and at risk of not having mounted an adequate immune response to vaccination against COVID-19; and
6 Not to be used in conjunction with other COVID-19 antiviral treatments

*Note: Patients at risk of severe illness from COVID-19, excluding pregnancy, as described on the Ministry of Health website
**or saturations no lower than baseline for patients with chronic resting hypoxia

5.4. 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.

5.5. The 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.

Discussion

The product:

5.6. The Group noted that Pfizer's oral protease inhibitor, nirmatrelvir reversibly inhibits the SARS-CoV-2 M^{pro} (Main protease) or 3-chymotrypsin-like-protease ($3CL^{pro}$) and that M^{pro} is essential for viral replication. The Group noted that the nirmatrelvir is co-packaged with ritonavir which as a pharmacokinetic enhancer, prolongs effective nirmatrelvir concentrations and is essential for co-administration with nirmatrelvir to ensure treatment efficacy. The Group noted that ritonavir is a strong inhibitor of CYP3A (with lesser effects on other CYP isoenzymes, eg. 2D6, 2B6, 2C9). The Group noted that the dose of ritonavir is 100 mg twice daily for five days (taken in combination with the nirmatrelvir) and that this dose would produce the maximal, or near maximal CYP3A inhibition. The Group noted that this inhibition has rapid onset with peak at 2-3 days of exposure, and recovery at approximately four days after discontinuation.

5.7. The Group noted that a large number of medicines are metabolised by CYP3A and therefore that the inclusion of this dose of ritonavir was likely to create complexities and restrictions in its use. Members noted the potential for clinically important drug-drug interactions with medicines used for mental health disorders, cardiovascular disease, cancer therapies, epilepsy, recreational drug users, and those who are immunosuppressed (eg people who have had transplants, those who are being treated for tuberculosis or living with HIV, cystic fibrosis, asthma or chronic pain, including on the methadone substitution programme). The Group noted that a large proportion of people classified as 'high risk' of developing severe illness (as per Ministry of Health advice) may be taking these medicines and as such this would impact the eligible patient pool. Members noted that there was limited information available to indicate the number of people screened but excluded from the clinical trial (EPIC-HR) due to co-prescribed medicines.

5.8. The Group noted that co-administration of relevant products with ritonavir would be expected to alter their pharmacokinetic profile (ie clearance) that could cause high concentrations and toxicity. The Group noted that for some co-administered drugs, such as methamphetamine, the increased concentrations could be lethal. Noting this, the Group considered that education for clinicians on the appropriate use of nirmatrelvir with ritonavir would be critical.

5.9. Members considered that some patients may need to consider stopping the use of other medicines when taking nirmatrelvir with ritonavir to minimise the risks associated with drug interactions; however, that this may not always be feasible and a case-by-case clinical impact assessment should occur prior to the initiation of treatment. The Group noted that pragmatic, practical, and standardised guidance would be important to ensure appropriate use.

5.10. The Group noted that as nirmatrelvir with ritonavir must be started within five days of symptom onset – if other medicines metabolised by CYP3A cannot be rapidly titrated down within the required time period, nirmatrelvir with ritonavir treatment would be redundant. Members considered that in the community, it is likely that health care professionals would be working within a window of one to two days to initiate nirmatrelvir with ritonavir, noting the time between symptom onset and test results.

5.11. The Group considered that nirmatrelvir with ritonavir could appropriately be prescribed and administered in a primary care setting. However, the Group noted the complexities of drug interactions and as such it would be preferable if either the patient's regular primary care clinician, or an experienced physician with access to the list of the patient's regular medicines and co-morbidities was the prescriber, to ensure that appropriate guidance and care is given. Members considered that if a patient was not on any other medicines, that it would be appropriate for any health care professional to prescribe nirmatrelvir with ritonavir in the community.

Evidence:

5.12. The Group noted the reported interim data from the EPIC-HR trial which investigated the use of nirmatrelvir with ritonavir in non-hospitalised adults with mild to moderate COVID-19 who had at least one characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (Pfizer media release November 2021; NCT04960202).

5.12.1. Where treatment was initiated three days after symptom onset, 0.8% of patients who received nirmatrelvir with ritonavir were hospitalised (3/389 hospitalised with no deaths) vs 7.0% of patients who received placebo and were hospitalised or died (27/385 hospitalised with 7 subsequent deaths), p<0.0001. Similar results were seen where treatment was initiated five days after symptom onset - 1.0% of patients who received nirmatrelvir with ritonavir were hospitalised (6/607 hospitalised, with no deaths) vs 6.7% of patients who received a placebo (41/612 hospitalised with 10 subsequent deaths), p<0.0001.

5.12.2. The Group noted the exclusion criteria included (but was not limited to) pregnancy, use of any medications or substances that are highly dependent on CYP3A4, and prior COVID-19 vaccination.

5.12.3. The Group noted that it was unclear which variants of COVID-19 were circulating at the time that the trial was undertaken.

5.13. The Group noted that at the time of review (13 December 2021), only interim data were available which had been included in a media release, however no data had been published in a peer reviewed journal. The Group considered that this evidence was therefore of low quality.

5.14. The Group also noted that two trials were ongoing which investigated nirmatrelvir with ritonavir in adults with COVID-19 who were at low risk of progressing to severe illness (EPIC-SR; NCT05011513) or in adult asymptomatic household contacts of an individual with symptomatic COVID-19 (EPIC-PEP; NCT05047601). Members considered that it was likely that the efficacy of nirmatrelvir with ritonavir may be diluted in these wider groups (eg. number needed to treat (NNT) would be higher).

5.15. The Group considered, that based on the available data, the population who would most likely benefit from nirmatrelvir with ritonavir would be those with COVID-19 not requiring supplemental oxygen, are at risk of progressing to severe illness, and unvaccinated or seronegative individuals (although noted there were no data available of the serostatus of trial participants).

5.15.1. Members noted that serology tests are not readily accessible in New Zealand at this point in time, particularly where a short turn around is required for treatment initiation and as such, did not consider that serostatus should be included as an access criterion to nirmatrelvir with ritonavir.

5.15.2. Members noted that while available data were in an unvaccinated patient population, there was no pharmacological reason that nirmatrelvir with ritonavir could not be used to treat vaccinated individuals with COVID-19.

5.16. The Group noted that Pharmac has estimated that 26% of symptomatic cases could be deemed as 'high risk' using an age proxy of ≥ 40 years, as evidenced by the elevated rate of hospitalisation observed in ≥ 40 year olds in the current outbreak (as of 11 November 2021). Members noted an alternative estimate of 24% of symptomatic cases could be deemed as high risk, estimated from a modelling study which reported 24% of the Oceanic population have at least one co-morbidity placing them at increased risk of severe COVID-19 (Clark et al. Lancet Glob Health. 2020 Aug;8(8):e1003-e1017). Members considered that the estimates provided were likely an underestimate for New Zealand as the modelling study did not take into account obesity. Members considered that a higher estimate should be used to reflect this, for example as high as 40%, noting that in 2020/21 around 1 in 3 New Zealanders (aged 15+ years) were classified as obese (Body Mass Index of ≥ 30) (Ministry of Health. 2021).

5.17. The Group noted that data as at November 2021, Māori and Pacific peoples accounted for 74% of all COVID-19 cases, which is a higher proportion than seen in 2020 (Ministry of Health. December 2021). The Group considered that this further demonstrates that Māori and Pacific ethnicity is a risk factor for developing symptomatic COVID-19. The Group noted that while case numbers were higher for Māori and Pacific people than other ethnic groups, hospitalisation rates were disproportionate. Members discussed that this data and resulting variation is influenced by many confounders and may be explained by disparities such as barriers to accessing healthcare services, as well as unconscious bias within the health system. The Group noted that currently the Ministry of Health's guidance on those at higher risk of the effects of COVID-19 includes Māori and Pacific ethnicity (Ministry of Health. December 2021).

5.18. The Group considered that while the Ministry of Health's guidance does include ethnicity as a risk factor, it was important to include Māori and Pacific ethnicity specific criterion in the Special Authority to improve any unnecessary and/or biased access barriers and to allow for evaluation of equitable treatment uptake.

5.19. The Group considered that, based on the limited available evidence, while nirmatrelvir with ritonavir and molnupiravir have a similar therapeutic effect, nirmatrelvir with ritonavir appeared to be more active (and therefore effective), than molnupiravir. However, the Group noted that the two trials assessing molnupiravir and nirmatrelvir with ritonavir, while undertaken in similar high-risk patient groups, substantially differed in the placebo-arm outcomes, namely

hospitalisations. Members considered that this made it difficult to directly compare the two drugs and considered that more data would better inform any comparison.

5.20. Members considered that there would be less risk for mutation development with nirmatrelvir with ritonavir due to the mechanism of action. The Group noted that nirmatrelvir with ritonavir and casirivimab/imdevimab have a different therapeutic effect, but similar therapeutic outcomes. The Group considered that nirmatrelvir with ritonavir has a suitability benefit over casirivimab/ imdevimab due to ease of administration as an oral treatment rather than an intravenous/subcutaneous infusion.

5.21. The Group considered that based on available evidence treatment with nirmatrelvir with ritonavir was inferior to vaccination against COVID-19 and noted there is considerable uncertainty regarding the efficacy of all COVID-19 therapeutic agents, including nirmatrelvir with ritonavir against current and future COVID-19 variants.

Modelling:

5.22. The Group noted that Pharmac has secured 60,000 courses of nirmatrelvir with ritonavir, to arrive in 2022 subject to Medsafe approval. The Group considered the 60,000 courses ordered was appropriate, noting the exclusions that would result due to drug-drug interactions and that additional courses of alternative oral antiviral agents had also been ordered.

5.23. The Group considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for nirmatrelvir with ritonavir if it were to be funded in New Zealand.

Population	Adults with acute COVID-19 disease (≤5 days from symptom onset) at high risk of progressing to severe disease, who do not require supplemental oxygen and have not completed the full primary vaccination schedule for COVID-19 (or are immune compromised and at risk of not having mounted an adequate immune response to vaccination).
Intervention	Nirmatrelvir with ritonavir, individual treatment course twice daily for five days
Comparator(s) (NZ context)	Best standard of care Molnupiravir
Outcome(s)	Reduced mortality Reduced hospitalisations Reduced infection rates Reduced hospital stay Improved time to recovery
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.	