Record of the COVID-19 Treatments Advisory Group Meeting held via video conference on 13 December 2021

Note that this document is not necessarily a complete record of the COVID-19 Treatments Advisory Group meeting held on 13 December 2021; rather it is a summary of the pertinent discussion at the meeting relating to one item. Further records from this meeting will be published in due course.

Present from the COVID-19 Treatments Advisory Group
Jane Thomas
Brian Anderson
Tim Cutfield
Eamon Duffy
Gillian Hood
Jessica Keepa
Stephen Munn
Marius Rademaker
Nigel Raymond
Justin Travers

Observers
Dan Bernal
Anne Buckley
Robyn Manuel

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

Application

1.1. 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.

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

Recommendation

1.3. The 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 immunocompromised 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

1.4. 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.

1.5. 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:

1.6. 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.

1.7. 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.

1.8. 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.

1.9. 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.

1.10. 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.

1.11. 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:

1.12. 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).

1.12.1. 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.

1.12.2. 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.

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

1.13. 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.

1.14. 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).

1.15. 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).

1.15.1. 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.

1.15.2. 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.

1.16. 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).

1.17. 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).

1.18. 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.

1.19. 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.

1.20. 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.

1.21. 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:

1.22. 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.

1.23. 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 immunocompromised 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:

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.