RATIONALE FOR UPDATED TASKFORCE RECOMMENDATION ON THE USE OF MOLNUPIRAVIR (LAGEVRIO)

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NATIONAL CLINICAL EVIDENCE TASKFORCE

COVID-19

2 DECEMBER 2022

SUMMARY OF TASKFORCE RECOMMENDATIONS FOR TREATING ADULTS WITH MILD COVID-19

In people with mild COVID at risk of developing severe disease:

- Consider using nirmatrelvir plus ritonavir (Paxlovid), remdesivir (Veklury) or tixagevimab plus cilgavimab (Evusheld)**
- Do not routinely use molnupiravir or sotrovimab
- Do not use azithromycin, colchicine, convalescent plasma, favipiravir, hydroxychloroquine, interferon beta-1a, ivermectin or lopinavir-ritonavir.

***The Taskforce is aware of concerns about the potential for decreased effectiveness of Evusheld (tixagevimab plus cilgavimab) against the BA.4 and BA.5 Omicron sub-variants, based on in vitro data. Recommendations will be updated when definitive evidence becomes available.*

What was the Taskforce's previous position on molnupiravir?

- Early results from the MOVe-OUT trial (a randomised, placebo controlled, blinded trial with >1,000 participants) suggested that there might be some benefit from molnupiravir in reducing mortality.
- However, the certainty of evidence was considered to be low, in part because the benefit was only seen during the first half of the trial. Its generalisability to the current situation is uncertain as the trial was conducted in unvaccinated participants during the Delta wave.
- Given the limitations of the evidence from MOVe-OUT, in early 2022 the Taskforce made a consensus recommendation that molnupiravir be considered for use in adults who were at high risk of severe outcomes from COVID-19, only where other drugs like nirmaltrevir plus ritonavir and remdesivir weren't available or suitable. A consensus recommendation is used when there is not enough evidence to give an evidence-based recommendation, but the Taskforce still regards it as important to give a recommendation based on expert opinion.
- Nirmatrelvir plus ritonavir, remdesivir and tixagevimab plus cilgavimab** were considered to be preferable because there was greater certainty of evidence demonstrating clinical benefit.

***The Taskforce is aware of concerns about the potential for decreased effectiveness of Evusheld (tixagevimab plus cilgavimab) against the BA.4 and BA.5 Omicron sub-variants, based on in vitro data. Recommendations will be updated when definitive evidence becomes available.*

What has changed?

- A trial of molnupiravir called PANORAMIC has been published as a preprint.
- This very large (25,783 participants) open-label randomised controlled trial was conducted in the UK, in patients who had multiple SARS-CoV-2 vaccine doses, during the Omicron wave, comparing molnupiravir to standard care.
- Our Drug Treatments Panel, Care of Older People Panel, Expert Advisors in Aged Care, Guidelines Leadership Group and Steering Committee have considered this research, and are also aware of observational data from the Victorian Department of Health.

What do we know now?

- From the PANORAMIC trial, there is high certainty evidence that molnupiravir does not have an impact on the combined endpoint of hospitalisation and/or mortality in multiply-vaccinated adults with mild COVID-19 and one or more risk factors for disease progression. Approximately 95% of participants had received three or more doses of SARS-CoV-2 vaccine prior to treatment.
- In the PANORAMIC trial there was no difference in incidence of serious adverse events between the molnupiravir and control arms.

- The PANORAMIC trial results strengthens our original position that nirmaltrelvir plus ritonavir, remdesivir and tixagevimab plus cilgavimab** are the preferred treatments for mild COVID, and that molnupiravir is not for routine use. ›
  ***The Taskforce is aware of concerns about the potential for decreased effectiveness of Evusheld (tixagevimab plus cilgavimab) against the BA.4 and BA.5 Omicron sub-variants, based on in vitro data. Recommendations will be updated when definitive evidence becomes available.*
- The Pharmaceutical Benefits Advisory Committee (PBAC) recently recommended (24/11/22) that an Administrative Note be added to the molnupiravir listing stating that molnupiravir should be considered for use only if nirmatrelvir and ritonavir is contraindicated or otherwise unsuitable (PBAC - Outcome Statement).

When might the use of molnupiravir be considered?

There is less evidence about the effect of molnupiravir in the highest risk patients, and in some settings, such as residential aged care. Although evidence regarding the use of other treatments (such as nirmatrelvir plus ritonavir and remdesivir) in these populations is also limited, current evidence provides greater certainty of benefit for these antiviral agents in the broader population, so use of these other antivirals rather than molnupiravir is preferred. However, there may be specific circumstances for the highest risk patients, where all other treatment options are contraindicated or inappropriate, in which non-routine use of molnupiravir might be considered, in consultation with specialist clinicians where necessary.

Was a reduction in symptom duration considered as an outcome?

Yes, our panels did consider the data in PANORAMIC suggesting potential reduction in time to first recovery. While the PANORAMIC trial reported a reduction in duration of symptoms in those receiving molnupiravir, this data should be interpreted with caution as time to recovery is a subjective, self-reported outcome in an open-label trial. Furthermore, molnupiravir was not associated with a reduced duration of symptoms in the placebo-controlled, blinded, MOVe-OUT trial.

Was a reduction in viral load considered?

The Taskforce considers evidence which addresses the clinical impacts of treatments on patient-relevant outcomes. Given this, we do not consider data addressing viral load, however we acknowledge that these outcomes may be important for those responsible for developing public health guidelines.

Was observational data considered?

The Taskforce is aware of a number of retrospective observational cohort studies describing the use of molnupiravir in a variety of populations and contexts (including Victoria). The nature of these studies means that their results are open to significant bias (particularly selection bias) and substantial confounding (both the healthy user effect and confounding by indication) and cannot provide reliable evidence to determine the effectiveness, or otherwise, of molnupiravir. However, these studies are very helpful in generating hypotheses, particularly about groups most likely to benefit from treatment, for testing in future randomised controlled trials.

The Victorian observational data has been reviewed by our expert biostatistical methods advisors, and, as per our standard methods, given the substantial risk of bias in observational studies, not formally included in our evidence-to-decision framework.

View our Technical Report for more information on our methods and processes.

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Was cost effectiveness considered?

The Taskforce does not consider cost-effectiveness in developing our recommendations, our focus is on clinical effectiveness, and the balance of clinical benefits and harms. Our recommendations are made based on which drugs are likely to have clinical benefits, based on the evidence and clinical expertise, regardless of cost.

How does the Taskforce guidance compare to international guidance?

- The UK National Institute for Health and Care Excellence (NICE) no longer supports use of molnupiravir in draft guidance published 16/11/2022:
  "Molnupiravir is not recommended, within its marketing authorisation, for treating mild to moderate confirmed COVID-19 in adults who have at least 1 risk factor for developing severe COVID-19." (https://www.nice.org.uk/guidance/gid-ta10936/documents/129)
- WHO and NIH positions have not been updated since the PANORAMIC trial was released.

What is still unknown?

- Patients at the highest risk of adverse outcomes from COVID-19** were not the target population of the PANORAMIC trial (although some were included), as in the UK these patients had been advised to access treatment directly though COVID-19 specialist clinics. Therefore, there is less evidence about the effect of molnupiravir in these highest risk patients, including those who are highly immunosuppressed, and in some settings such as residential aged care.

  ***The definition of highest risk (https://www.gov.uk/government/publications/highest-risk-patients-eligible-for-covid-19-treatments-guide-for-patients/highest-risk-patients-eligible-for-new-covid-19-treatments-a-guide-for-patients) includes people with Down's syndrome, leukaemia or lymphoma, sickle cell disease, chronic kidney disease (CKD) stage 4 or 5, severe liver disease, who had an organ or bone marrow transplant, advanced HIV disease, multiple sclerosis, motor neurone disease, Huntington's disease or myasthenia gravis, cerebral palsy, or a weakened immune system due to a medical treatment (including biological therapy, chemotherapy or radiotherapy).*

- Data collection continues for longer term outcomes in PANORAMIC, and this may provide information on important outcomes such as development of long-COVID.
- Other trials, ideally placebo-controlled, could provide more reliable evidence about the impact of molnupiravir or other treatments on duration of symptoms.
- The impact of molnupiravir on outcomes such as viral load and transmission is not yet clearly established, and as discussed above were not considered to be in scope for the Taskforce clinical guidelines. Further, reliable data for these outcomes might be helpful in determining the public health benefits of molnupiravir use.
- PANORAMIC is currently evaluating the effectiveness of nirmatrelvir plus ritonavir in patients who had received multiple vaccine doses and Taskforce recommendations will be updated when these data become available.
- We don't currently have reliable evidence to evaluate the comparative effectiveness of the available treatments for people with mild COVID-19, or evidence to evaluate the effectiveness of combination treatments.

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What does the Taskforce now recommend on use of molnupiravir?

Conditional recommendation against

Updated

Do not routinely use molnupiravir for the treatment of COVID-19

Additional information

Preliminary results of the PANORAMIC trial in 25,783 participants with the Omicron variant provide high certainty evidence that molnupiravir does not have an impact on the combined endpoint of hospitalisation and/or mortality in multiply-vaccinated* adults with mild COVID-19 and one or more risk factors for disease progression.

Patients at the highest risk of adverse outcomes from COVID-19** were not the target population of the PANORAMIC trial (although some were included), as in the UK these patients had been advised to access treatment directly though COVID specialist clinics. Therefore, there is less evidence about the effect of molnupiravir in these highest risk patients, and in some settings such as residential aged care.

Although evidence regarding the use of other treatments (such as nirmatrelvir plus ritonavir, and remdesivir) in the highest risk patients is also limited, current evidence provides greater certainty of clinical benefit for other antiviral agents in the broader population; therefore use of these other antivirals agents rather than molnupiravir is preferred. However, there may be specific circumstances for the highest risk patients, where all other treatment options are contraindicated or inappropriate, in which non-routine use of molnupiravir might be considered, in consultation with specialist clinicians where necessary.

**Approximately 95% of participants had received three or more doses of SARS-CoV-2 vaccine prior to treatment and a high proportion had likely experienced previous infection.*

***Definition of highest risk (https://www.gov.uk/government/publications/highest-risk-patients-eligible-for-covid-19-treatments-guide-for-patients/highest-risk-patients-eligible-for-new-covid-19-treatments-a-guide-for-patients) includes people with Down syndrome, leukaemia or lymphoma, sickle cell disease, chronic kidney disease (CKD) stage 4 or 5, severe liver disease, organ or bone marrow transplant, advanced HIV disease, multiple sclerosis, motor neurone disease, Huntington's disease or myasthenia gravis, cerebral palsy, or a weakened immune system due to a medical treatment (including biological therapy, chemotherapy or radiotherapy).*

*This is a **high priority** recommendation and will be updated as soon as new evidence becomes available.*