NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Molnupiravir for treating COVID-19

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using molnupiravir in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: November 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using molnupiravir in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 17 December 2024
- Second evaluation committee meeting: 11 February 2025
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Molnupiravir is not recommended, within its marketing authorisation, for treating mild to moderate COVID-19 in adults who have:

- a positive SARS-CoV-2 test, and
- 1 or more risk factors for developing severe COVID-19.

Why the committee made these recommendations

Usual treatment for mild to moderate COVID-19 in people at risk of developing severe COVID-19 includes nirmatrelvir plus ritonavir, or sotrovimab when nirmatrelvir plus ritonavir is unsuitable. There are no other treatment options when these medicines cannot be used.

The company asked for molnupiravir to be considered only in the community setting for people with mild to moderate COVID-19 who are at risk of developing severe COVID-19 and cannot have nirmatrelvir plus ritonavir, or sotrovimab. This does not include everyone it is licensed for.

Some results from clinical trials and real-world evidence for the people molnupiravir is licensed for suggest that it reduces the likelihood of hospitalisation or death compared with no treatment. But results from the UK do not show clinically meaningful effects with molnupiravir compared with no treatment. The evidence the company submitted is not specific to people with the highest risk of developing severe COVID-19. Also, who this includes is uncertain.

Because of these uncertainties, it is not possible to determine the most likely cost-effectiveness estimates for molnupiravir. So, molnupiravir is not recommended.

2 Information about molnupiravir

Marketing authorisation indication

2.1 Molnupiravir (Lagevrio, Merck Sharp & Dohme) is indicated 'for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in

adults with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for molnupiravir.

Price

2.3 The list price for molnupiravir is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Merck Sharp & Dohme, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Impact of COVID-19 and access to treatment

3.1 COVID-19 is an acute respiratory illness caused by the SARS-CoV-2 virus. It can range from mild to severe. In severe COVID-19, excessive immune response to the virus may cause severe complications that are associated with hospitalisation and death. The need for organ system support, particularly respiratory support, is also a key feature of severe COVID-19 and can be associated with substantial longer-term morbidity. COVID-19 may also cause long-term symptoms that continue or develop after acute infection. This is called 'long COVID' and causes health problems that fluctuate and can last several months or years. A patient expert explained how long COVID affects all aspects of their life. It means that they have constant fatigue, pain and often became breathless after only moderate activity. They explained that, even if they have good days when they can be more active, this then results in them being particularly exhausted the day after. Many people are at increased risk of hospitalisation or death from COVID-19, including people:

- who are immunocompromised, for example, people with primary immunodeficiency
- having chemotherapy
- who have had a transplant and may have medication to prevent organ rejection
- with comorbidities such as heart disease, respiratory disease, diabetes or neurological conditions.

Some people who are immunocompromised are at risk of persistent viral infection if their immune system cannot control the virus. A second patient expert explained that people at higher risk of severe COVID-19 use a range of behaviours to try and avoid infection. For most people, this includes using face masks and avoiding crowds. But, for people at the highest risk (such as people who have had a lung transplant), this might involve almost complete self-isolation. Patient-expert submissions highlighted the need for treatment options for COVID-19, particularly in people at high risk. They explained that there are very few treatment options available, some of which are difficult to access. A clinical expert also highlighted variation in clinical management depending on severity. They thought that molnupiravir might address an unmet need for an alternative oral treatment option for COVID-19. The committee noted that the risk of COVID-19 infection is significantly lower than during the pandemic phase. t understood that the risk of hospitalisation and death, and other longer-term impacts of COVID-19, result in severe mental burden, and infection can still have serious physical effects. It concluded that people at high risk of severe COVID-19 would welcome new and effective treatment options.

The rapidly evolving SARS-CoV-2 virus

3.2 The global COVID-19 pandemic caused unprecedented challenges to the healthcare system. This is reflected in the evidence collected on COVID-19 and the treatments for it. The SARS-CoV-2 virus evolved during the

pandemic, as did the healthcare system's ability to respond to the virus. New variants and subvariants (variants of concern) emerged, the properties of which differed, such as levels of transmissibility and disease severity. The clinical experts explained that the situation around COVID-19 changed during the pandemic, with:

- increasingly effective supportive care
- growing numbers of people having vaccination
- rising natural immunity.

The committee understood that, since the beginning of the pandemic, overall hospitalisation and mortality rates from COVID-19 have fallen because of improved clinical management. It also noted the changing nature of SARS-CoV-2 and the context of the pandemic. It thought that the shift to an endemic situation might affect the generalisability of the evidence for this evaluation (see section 3.6).

Clinical management of COVID-19

Defining high-risk populations

3.3 The risk of developing severe COVID-19 is associated with age, sex, and various other factors and comorbidities. In the UK, factors for defining high risk of progression to severe COVID-19 are listed in:

- the independent advisory group report commissioned by the Department of Health and Social care definition (from here, the McInnes definition)
- the Therapeutics Clinical Review Panel risk of severe COVID-19 outcomes report definition (from here, the Edmunds definition) list.

Both of these definitions have been used to inform recent clinical decision making. The McInnes report definition covers adults with a range of health conditions (see section 5 of NICE's technology

appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19 [from here, TA878]). The Edmunds definition covers the same factors as the McInnes definition and also age over 70 years, diabetes, having a body mass index of over 35 and heart failure. The committee noted that the marketing authorisation for molnupiravir is for people with at least 1 risk factor for developing severe illness. It thought that, in practice, the marketing authorisation population would include anyone covered by the Edmunds or McInnes definitions.

Treatments for mild to moderate COVID-19

3.4 Current clinical management for COVID-19 in adults includes nirmatrelvir plus ritonavir, sotrovimab (see TA878) and remdesivir (see NICE's technology appraisal guidance on remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [from here TA971]). They are options for treating COVID-19 for people who do not need supplemental oxygen and have an increased risk for progression to severe COVID-19 (risk factors as defined in section 5 of TA878). Sotrovimab is used only if nirmatrelvir plus ritonavir is contraindicated or unsuitable. Remdesivir is recommended as an option for treating COVID-19 in hospitals only. Molnupiravir is, at the time of this evaluation, available through an NHS Interim Clinical Commissioning Policy for COVID-19 in people at high risk according to the McInnes definition, if nirmatrelvir plus ritonavir and sotrovimab are contraindicated or unavailable. People who have symptoms and are not showing signs of a clinical recovery should start treatment as soon as possible after testing positive for COVID-19. But the clinical and patient experts at the committee meeting highlighted the variability in access to the treatment options for COVID-19. The clinical experts explained that this variability in access to treatment was because of several factors including:

- geographical location
- different clinical approaches

- differences between clinical specialities in managing COVID-19 in people at risk
- variability in self-tested and healthcare-professional-tested lateral flow tests.

A patient expert explained that, among people at high risk, there was variation in access to treatment. They added that people who are more knowledgeable about the healthcare system may be more likely to access antiviral treatments. The committee considered the treatment options available and acknowledged that there is variability in the access to them.

Proposed positioning of molnupiravir

3.5 The company submission initially positioned molnupiravir in the community setting, to be used:

- as an alternative to nirmatrelvir plus ritonavir for people at risk of severe COVID-19 in line with the McInnes or Edmunds criteria
- when nirmatrelvir plus ritonavir is contraindicated for people at risk of severe COVID-19 in line with the Edmunds criteria, when there is currently no treatment option available
- when nirmatrelvir plus ritonavir is contraindicated for people at risk of severe COVID-19 in line with the McInnes criteria, as an alternative to sotrovimab.

The company submission did not provide any analysis for people who caught COVID-19 while already hospitalised, because there was a lack of relevant data. The EAG clinical expert agreed that there is limited data for this population. Remdesivir (which was subject to NICE evaluation) was a comparator listed in the final scope for this evaluation. But the company submission did not think that it was a relevant comparator. This was because TA971 recommends remdesivir as an option for treating COVID-19 in the hospital setting only. Ahead

of the evaluation committee meeting, the company proposed a new treatment position for molnupiravir. This was for people covered by the Edmunds or McInnes criteria for whom nirmatrelvir plus ritonavir is contraindicated, or sotrovimab is contraindicated, unfeasible or undesirable. So, this is when the only alternative would be no treatment. The company thought that this positioning would be in line with the NHS Interim Clinical Commissioning Policy (see section 3.4). The committee questioned why the company had proposed a new position for molnupiravir. The company responded that it thought that the strongest clinical evidence was molnupiravir compared with no treatment. A clinical expert said that the population at highest risk of severe COVID-19 (defined by the McInnes criteria), who could not have either nirmatrelvir plus ritonavir or sotrovimab, was likely small. They said that contraindication would be the most common reason for not having nirmatrelvir plus ritonavir because of the risk of drug-to-drug interactions with chemotherapy for cancer or medication to prevent organ transplant rejection. They thought that not being able to have sotrovimab would likely be because of people not being able to travel to hospitals or clinics for an infusion. The patient expert said that people should be able to have sotrovimab in their own homes. But both they and the clinical expert acknowledged that access to this type of administration was very variable. The patient expert was also concerned that a positive recommendation for molnupiravir (administered orally) in the population for whom sotrovimab was unfeasible might mean that the NHS would be even less likely to provide home administration of sotrovimab. They thought that, if molnupiravir was inferior to sotrovimab, this could disadvantage some people.

The committee noted that the proposed positioning was not in line with the NHS interim commissioning policy (see section 3.4). This policy states that molnupiravir should only be used when nirmatrelvir plus

ritonavir and sotrovimab are contraindicated or clinically unsuitable in the group at highest risk for severe COVID-19, as defined by the McInnes criteria. The committee noted that nirmatrelvir plus ritonavir is recommended by NICE for people covered by the Edmunds criteria. But, in practice, few people have access to it because of the funding variation that is in place. The committee thought that people covered by the McInnes criteria who cannot have either of the available treatments remain at increased risk of poor outcomes and have the greatest unmet need. It concluded that this population (from now, the 'highest unmet need' population) was the most appropriate for decision making. But it thought that there was uncertainty around exactly how the subpopulation who could not have nirmatrelvir plus ritonavir or sotrovimab was defined. It concluded that it would need to see additional evidence that better defined the highest unmet need population, including why these treatments would be contraindicated and why sotrovimab might not be feasible or desired. It also concluded that it needed to see updated evidence on the clinical effectiveness of molnupiravir in this highest unmet need population (see sections 3.7 to 3.9).

Clinical effectiveness

Generalisability of the clinical-effectiveness evidence

3.6 The committee recalled:

- the evolving nature of the SARS-CoV-2 virus
- the move from a pandemic to an endemic setting with improved clinical management for COVID-19
- the reduced hospitalisation and death rates (see section 3.2).

It questioned whether there could be issues of generalisability with evidence that was generated at different points in time. The clinical experts thought that a key period in time was late 2021 to early 2022.

Around this time, the Omicron variant became dominant in the UK and most people started to have the third dose of a COVID-19 vaccine. In early 2022, there was also wider rollout of antiviral treatments. The clinical experts thought that the situation in late 2021 to early 2022 and beyond was broadly similar to the situation today. They added that they would expect similar results if studies from early 2022 were done again now. They acknowledged that there are different variants of Omicron, which might behave differently, but are all broadly similar. The clinical experts thought that studies done from late 2021 onwards would likely be generalisable to the endemic situation at the time of this evaluation. The committee noted this. It thought that it was likely that studies done from 2022 onwards would be generalisable to the current clinical setting. But it thought that it was plausible that there would be some uncertainty when using these studies to reflect clinical practice. The committee thought that there could also be generalisability issues based on geographical location and the risk level used for study recruitment. It noted that the network meta-analyses (NMAs) of real-world evidence (RWE; see section 3.9) only included 1 UK study (Zheng et al. 2023). The committee concluded that it would take generalisability into account in its decision making.

Randomised clinical trial evidence

3.7 In the company submission, evidence from 2 randomised controlled trials (RCTs), MOVe-OUT and PANORAMIC, was used to inform some model parameters in the company's economic model (see section 3.11). Move-OUT (n=1,433) was a company-sponsored, phase 2 and 3, multicentre (including 6 UK centres), double-blind RCT comparing molnupiravir with placebo. It included adults who:

- were not in hospital
- tested positive for SARS-CoV-2
- presented with mild to moderate symptomatic COVID-19

- had at least 1 risk factor for progression to severe COVID-19.

The trial reported a 6.8% (95% confidence interval [CI] -11.3 to -2.4) reduction in all-cause hospitalisation or death for molnupiravir compared with placebo in the interim analysis and 3% (95% CI -5.9 to -0.1) reduction in the final analysis. PANORAMIC (n=26,411) was a large, UK-only, primary care, open-label, multigroup, prospective, platform-adaptive trial comparing molnupiravir with usual care. It included people with COVID-19 symptoms and a positive SARS-CoV-2 test who were not in hospital and were 50 years or over, or 18 years or over and had comorbidities. The primary outcome was all-cause hospitalisation or death at day 29 (odds ratio 1.06, 95% CI 0.81 to 1.41). The committee noted that MOVe-OUT was done from May to October 2021. It recalled the clinical expert testimony about generalisability (see section 3.6). The committee thought that MOVe-OUT was not generalisable to current clinical practice, so was not appropriate to inform the model (see section 3.13). A clinical expert said that PANORAMIC was done in a population that had high levels of vaccination at a time when Omicron was becoming the dominant variant. The committee thought that PANORAMIC, being a large UK-based study done between December 2021 and April 2022 was likely to be generalisable to clinical practice (see section 3.6). It noted that it was a very large trial with the potential to provide reliable subgroup analyses. A clinical expert, an investigator on PANORAMIC, confirmed that inclusion criteria in PANORAMIC were broad. But, because the trial was so large, various subgroup analyses were still possible, including in people with diabetes, people with lung disease and people who were immunocompromised. The committee concluded that the overall population of PANORAMIC was not likely to reflect the highest unmet need population for molnupiravir (see section 3.5). But it would like to see PANORAMIC subgroups explored to inform the clinical

effectiveness of molnupiravir compared with no treatment in the highest unmet need population.

NMAs of RCT evidence

3.8 The company did NMAs of RCTs to enable molnupiravir to be compared indirectly with nirmatrelvir plus ritonavir, sotrovimab, remdesivir and no treatment. A total of 11 RCTs were included in the NMAs. The results of NMAs of RCTs for hospitalisation or death showed that molnupiravir was not statistically significantly superior to any comparator other than no treatment. The company did not use the NMAs of RCTs to inform the economic model because the trials were largely done before Omicron was the dominant variant (see section 3.7). The EAG agreed that the NMAs of RCTs had significant limitations including:

- the likely lack of generalisability
- the fact that the company had not adequately assessed the sensitivity of the NMAs of RCTs to risk of bias
- the fact that only fixed-effects models had been submitted, which meant that the uncertainty in the NMAs was possibly underestimated.

The committee considered the various limitations of the NMAs of RCTs and concluded that they were of limited use for decision making.

RWE and NMAs

3.9 The company also did pairwise NMAs of RWE studies comparing molnupiravir with nirmatrelvir plus ritonavir, sotrovimab, remdesivir or no treatment when sufficient RWE studies were available for each of these comparisons. The company identified 30 RWE studies, 17 of which were thought to be appropriate for inclusion in the NMA. The studies were of varying design, risk profile for severe COVID-19, geographical location, sample size, recruitment time period and outcomes. The results of these NMAs did not provide evidence that molnupiravir was significantly superior to any active comparator for any hospitalisation and death

outcomes. But it showed statistically significant superiority for all-cause hospitalisation or all-cause death when compared with no treatment. But there was no evidence that molnupiravir was clinically superior to no treatment for COVID-19-related hospitalisation or death. The EAG highlighted several uncertainties associated with the NMAs of RWE. These were:

- uncertainty around the appropriate time cut-off to ensure relevance of studies to clinical practice, and generalisability of NMA results
- a lack of UK studies included in the NMAs
- limitations of the clinical-effectiveness results of the NMAs because of a lack of results for outcomes for COVID-19 symptom progression or resolution, virological outcomes or the need for respiratory support
- uncertainty in the clinical significance of statistically significant reductions in hospitalisation rate.

The EAG also identified a UK study (Tazare et al. 2023) that was not identified by the company's literature review. This was a study using the OpenSAFELY database. It noted that this study reported no statistically significant difference between molnupiravir and no treatment for the outcome of COVID-19-related hospitalisation or death. The committee noted the uncertainties highlighted by the EAG and the additional study identified. It thought that the best available RWE evidence it had seen so far was likely to be Tazare et al. It also thought that, because of the updated positioning (see section 3.5):

- the only relevant comparison was with no treatment
- there was substantial uncertainty around whether the NMAs of RWE showed any significant benefit for hospitalisation or death outcomes for this comparison.

The committee also noted that the NMAs of RWE might not appropriately reflect the highest unmet need population. This was

because the studies included people with a range of different risks for severe COVID-19 and the highest unmet need population was specific to people with the highest risk (see section 3.5). It concluded that it would need to see either evidence that showed the NMAs of RWE reflected the highest unmet need population, or an updated NMA of RWE or new RWE evidence to inform the modelling of the highest unmet need population.

Risk of novel mutations and risk of resistance with molnupiravir

3.10 The committee was aware that molnupiravir has a mechanism of action that alters the RNA of the virus. This causes novel mutations of SARS-CoV-2 that may potentially be transmitted if the virus is not fully cleared. The clinical experts explained that viral clearance is necessary to avoid transmitting the virus and any viral mutations generated by the mechanism of action of molnupiravir. This could increase the risk of new SARS-CoV-2 variants developing and potentially reduce the efficacy of molnupiravir. The EAG noted that limited results for the virological outcomes from MOVe-OUT were reported by the company in its clarification response compared with the expected virological endpoints of the trial. The EAG highlighted that virological outcomes were only analysed in the NMAs of RCTs. These showed improved clearance compared with no treatment, although the results were subject to limitations (see section 3.7). A clinical expert said that molnupiravir has been shown to drive a pattern of mutagenesis that is identifiable in global circulating virus, particularly in areas where molnupiravir has been used. They noted that, in PANORAMIC, viral load was higher in the molnupiravir arm than the usual-care arm on day 14. The clinical expert said that there is an increased risk of immune-escape variants arising and persisting in people who are immunocompromised. This is because their immune systems are less likely to clear the virus fully. The committee noted that, with the new positioning of molnupiravir (see section 3.5), the highest unmet need population is likely to have a larger proportion of people who

are immunocompromised. It thought that there is a theoretical risk that molnupiravir use might increase the risk of new variants emerging and drug resistance. The committee thought that this was not something that could not be captured in the modelling, but that it could consider this in its decision making as a non-health factor.

Economic model

Company's modelling approach

3.11 The company developed a hybrid economic model comprising:

- a decision tree for the acute phase of COVID-19 (30 days), and
- a Markov model to follow people who survive the acute phase through their lifetime.

In the acute phase of the model, people in the outpatient setting started treatment with molnupiravir or 1 of the comparators. They then stayed in the outpatient setting, or were admitted to hospital because of severe COVID-19. In hospital, they could be in a general ward, a high dependency unit or an intensive care unit with mechanical ventilation (the highest level of care). The treatment effects of molnupiravir and the comparators included preventing progression to hospitalisation and reducing symptom duration. In hospital, the treatment effect of inpatient drugs (remdesivir and tocilizumab) was applied. People surviving the acute phase of COVID-19 and being discharged from hospital entered the Markov model. They could then either recover or experience long-term sequelae. There were some differences in assumptions used in the economic model between the company's and EAG's base cases. These included:

- The company modelled 51.3% women based on MOVe-OUT. The EAG modelled 59.0% women based on PANORAMIC.
- The company used a hospitalisation rate of 3.79% using all-cause hospitalisation from NMAs of RWE. The EAG used a hospitalisation

rate of 2.41% using COVID-19 related hospitalisation from OpenSAFELY.

- The company used health-state utility values based on a vignette study. The EAG used general population utilities adjusted for the relative decrements seen in Soare et al. (2024).
- The company assumed an acute mortality rate of 24.98% for the subgroup of people who are immunocompromised based on INFORM. The EAG highlighted that the mortality rate for people who are immunocompromised was likely a key model driver, particularly in a subgroup with a higher proportion of such people. Instead, it preferred a 10.39% acute mortality rate for this subgroup based on TA971.

The EAG highlighted that it was unclear how appropriate it was to assume that remdesivir is used to treat COVD-19 in people admitted to hospital because of the condition. Clinical advice to the EAG noted that NICE's COVID-19 rapid guideline on managing COVID-19 and TA971 lack detail on where in the treatment pathway remdesivir should be used or whether it is indicated for mild or severe symptoms. It also noted that they rarely use remdesivir in their clinical practice. The EAG also highlighted that the economic model did not capture the pathway of people with incidental COVID-19 (see section 3.5). This was because of a lack of specific data for this group, which was likely to be significant in size. But, overall, the EAG thought that the company's model structure was appropriate for decision making, and in line with previous cost-effectiveness studies for molnupiravir and other outpatient COVID-19 treatments. The committee concluded that the company's economic model structure was appropriate for decision making.

Hospitalisation rates

3.12 In its base case, the company used an all-cause hospitalisation rate of 3.79% from NMAs of RWE for people who have not had treatment. This

was because it was the primary outcome assessed across the studies included in the NMAs of RWE. The EAG noted that the outcomes in these NMAs also included COVID-19-related hospitalisation rates, which were lower than the all-cause hospitalisation rates. It explained that using a lower hospitalisation rate leads to a worse cost-effectiveness estimate for molnupiravir compared with no treatment. The EAG highlighted that there were no UK studies included in the NMAs that reported all-cause or COVID-19-related hospitalisation rates for people who have not had treatment. Zheng et al. (2023), a UK study done using the OpenSAFELY cohort, did not report data on this outcome because it did not include the untreated population. The EAG further explained that the committee for TA878 and TA971 thought that the hospitalisation rate for people who have not had treatment should be between 2.41% (estimate from OpenSAFELY) and 2.82% (estimate from DISCOVER-NOW). The EAG preferred the 2.41% COVID-19 related hospitalisation rate from OpenSAFELY in its base case. The clinical experts explained that COVID-19-related hospitalisation rates have come down in recent years. One clinical expert at the meeting highlighted that the rate of hospitalisation is uncertain but likely to be between that of the company's and EAG's base case. The clinical experts explained that there is a large variation in the risk profile of people at high risk of severe COVID-19. They added that this is likely to affect the hospitalisation rates, which would vary between high-risk subgroups. Another clinical expert highlighted that the rate of hospitalisation was much lower in PANORAMIC, although they noted that the full population for this trial included people who were not at high risk of severe COVID-19 according to the Edmunds definition. The committee noted that the company's and EAG's base-case values were specific to the initial marketing authorisation population. So, it thought that considering different hospitalisation rates should be explored if up-to-date hospitalisation rates for the highest unmet need population are available.

Treatment effect on hospitalisation

3.13 In its base-case economic model, the company modelled a treatment effect on hospitalisation. It did this using the relative risk of all-cause hospitalisation for molnupiravir compared with no treatment (0.79, 95% CI:0.66 to 0.92) from the NMAs of RWE (see section 3.9). The EAG highlighted that there were no UK studies included in these NMAs for all-cause hospitalisation. It also explained that the relative risk of COVID-19-related hospitalisation was based on a fixed-effect analysis because of the sparsity of the evidence network. So, the confidence intervals for the relative risks of COVID-19-related hospitalisation did not capture between-study heterogeneity. The EAG thought that it was unclear from a clinical point of view whether the treatment effect for all-cause hospitalisation or COVID-19-related hospitalisation should have been used in the economic model. The EAG also noted that the UK real-world studies, Zheng et al. (2023; see section 3.6) and Tazare et al. (2023; see section 3.9) did not report either of these outcomes. Instead, they reported a composite hospitalisation and death outcome that did not match the parameters in the company's economic model. The EAG thought that it was unclear whether outpatient treatments have any effect on mortality, noting that no such effect was modelled. It thought that, if there was no effect, it would be appropriate to use the composite outcomes from Tazare et al. to inform hospitalisation rates in the model. The EAG used the same approach as company in its base case but explored scenario analyses on the treatment effect on hospitalisation. These were a relative risk of:

- COVID-19-related hospitalisation from the NMAs of RWE for all the comparisons
- 1.0 for COVID-19-related hospitalisation or death based on the conclusions from Tazare et al. for the comparison with no treatment
- all-cause hospitalisation from the RWE direct meta-analysis
- 0.81 for the comparison with no treatment.

The committee thought that the treatment effect on hospitalisation for

molnupiravir for all comparisons was very uncertain. It thought that because of the highest unmet need population (see section 3.5) the only relevant comparison was with no treatment. With current evidence (for the wider population), it was unclear whether molnupiravir reduced hospitalisation compared with no treatment. The committee concluded that it would like to see various sources of clinical evidence explored, including the RWE NMAs (see section 3.9), PANORAMIC (see section 3.7) and single studies including Tazare et al. and the OpenSAFELY database (see section 3.9). This would be to see which provides the most appropriate estimate of relative effectiveness for the highest unmet need population.

Utility values

Source of utility values

3.14 In the company's base case, health-state utility values were informed by a vignette study done by the company. This involved members of the UK public completing EQ-5D-5L questionnaires for each of the model health states. The EAG thought that the utility values derived from the company's vignette study lacked face validity. This was because they were much lower than other sources and included negative values for people in hospital. The EAG also highlighted that the vignette study did not meet NICE's reference case. This was because it used members of the public rather than people with COVID-19 and carers to answer the questionnaire. Instead, the EAG used utilities from Soare et al. (2024) in its base case. This study reported EQ-5D-5L values for people with mild to moderate COVID-19 in the UK, including for pre-COVID, acute COVID, post-COVID and long COVID. The EAG also assumed:

- that a utility of 0.38 applied for people hospitalised with acute COVID-19, reflecting that for people on a general hospital ward (TA878 and TA971)

- a utility of 0 applied for people in an intensive care unit having mechanical ventilation (TA878 and TA971).

The committee noted that, in Soare et al., there was minimal difference in people's utility values before and after an episode of long COVID. It thought that this was implausible in light of the patient-expert testimony (see section 3.1). It also noted this was an opt-in internet study that may have been associated with negative bias and which could have underestimated disutility. The committee noted that the highest unmet need population (see section 3.5) was likely to include mainly people with pre-existing health conditions and comorbidities, who are already having treatments. It thought this may have affected quality of life, so additional evidence should be explored to ensure that the utility values used in the model reflect the highest unmet need population.

Severity

3.15 The committee considered the severity of the condition (that is, the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs; that is, a severity modifier) if technologies are indicated for conditions with a high degree of severity. Both the company and EAG thought that a severity weighting was not appropriate for the COVID-19 disease area. Even for the most vulnerable subgroups of people (immunocompromised or with chronic kidney disease), in line with the approach taken in TA971, a severity modifier was not applied. So, the committee concluded that NICE's methods on conditions with a high degree of severity did not apply.

Cost-effectiveness estimates

The committee's preferred assumptions

3.16 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per

QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will consider the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also consider other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, which arose from:

- the company's repositioning of molnupiravir in people who cannot have nirmatrelvir plus ritonavir, or sotrovimab, and uncertainty around the exact definition of the highest unmet need population (see section 3.5)
- the clinical effectiveness of molnupiravir compared with no treatment in the highest unmet need population (see sections 3.7 to 3.9 and section 3.13)
- the hospitalisation rates for people who have not had treatment in the highest unmet need population (see section 3.12)
- the risk of virus mutations associated with the mechanism of action and viral clearance profile of molnupiravir (see section 3.10)
- the utility values used for different health states for people in the highest unmet need population (see section 3.14).

The committee concluded that it could not establish its preferred cost-effectiveness estimates and threshold. It wanted to see a clear definition of the highest unmet need population (see section 3.5) and updated evidence specific to that population to inform the model.

Managed access

Recommendation with managed access

3.17 The committee noted that the company had not submitted a managed access proposal and there were no sources of data collection that would allow a managed access proposal. So, the committee could not make a recommendation for managed access.

Other factors

Equality

3.18 The company submission highlighted that molnupiravir supports the need for an easy-to-administer oral treatment for mild to moderate COVID-19. The aim is to provide options for people, particularly people with protected characteristics and to eliminate any residual and unobserved aspects of access inequality. The patient carer organisation said that most people eligible for molnupiravir are disabled in some way by their pre-existing condition. The clinical expert submission noted that molnupiravir is contraindicated during pregnancy, so a pregnancy test should be done before it is used. The committee thought that its recommendations do not have a different impact on people protected by the equality legislation than on the wider population. The committee concluded that there were no equalities issues that could be addressed by its recommendations.

Uncaptured benefits

3.19 The committee considered whether there were any uncaptured benefits of molnupiravir. It did not identify additional benefits not captured in the economic modelling. So, the committee concluded that all additional benefits of molnupiravir had already been considered.

Conclusion

Recommendation

3.20 The committee had concerns about how the highest unmet need population should be defined, particularly around why sotrovimab is contraindicated, unfeasible or undesirable. A clear definition of the highest unmet need population, and exploration of relative effectiveness and model inputs for this highest unmet need population, is needed before decisions can be made on the most appropriate modelling assumptions. So, the committee did not recommend molnupiravir as a treatment for mild

to moderate COVID-19 in adults who have a positive SARS-CoV-2 test, and 1 or more risk factors for developing severe COVID-19.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien
Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Zain Hussain
Technical lead

Samuel Slayen and Adam Brooke
Technical adviser

Louise Jafferally

Project manager

Ross Dent

Associate director

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