National Institute for Health and Care Excellence

Health Technology Evaluation

Molnupiravir for treating COVID-19 [ID6340]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Merck Sharp & Dohme (company)	MSD agree that a single technology appraisal is the correct route for the evaluation of molnupiravir.	Thank you for your comment. No action required.
Wording		No comments	
Timing issues	Merck Sharp & Dohme (company)	It is important for patients to have access to molnupiravir at the earliest opportunity for the following reasons: • Molnupiravir provides an alternative treatment for patients with mild to moderate disease at risk of developing severe disease. A number of patients are ineligible for currently available treatments due to contraindications, such as patients with severe renal and hepatic impairment.1 Patients taking certain medicines (for example anticoagulants, anticonvulsants and antiarrhythmics) are also at risk of drug-drug interactions (DDI) if prescribed nirmatrelvir plus ritonavir.1	Thank you for your comment. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible. No action is needed.

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		• Molnupiravir, can be administered orally unlike the recommended alternative for patients who are contraindicated to nirmatrelvir plus ritonavir (sotrovimab).2,3 Molnupiravir can thus be dispensed in a community setting for self-administration at home, reducing hospital resourcing and costs, and easing the patient experience. • The evolution of SARS-CoV-2 is unknown, therefore additional treatment options are needed to reduce future increases in disease burden	
	Forgotten Lives UK	This represents another effective tool in the ability to deal with Covid-19 infection for the most at risk. It is therefore essential that the evaluation of this is treated urgently, especially in light of the funding appeal for TA878, which could mean the availability of access to the full range of antivirals has been temporarily limited and therefore places further importance to this drug being made widely available.	Thank you for your comment. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible. No action is needed.
	LUPUS UK	This evaluation should go through a rapid process. Given that the COVID-19 virus evolves and different variants become dominant over time, it is critical that: 1. The treatment is evaluated while the evidence being considered is relevant, for example efficacy against particular variants. 2. The window during which the treatment is effective is not missed due to delays in evaluation. Although rates of COVID-19 are lower than they were at the height of the pandemic, many people who are at high risk (and would be eligible for Molnupiravir) are finding it increasingly difficult to protect themselves from infection as national precautionary measures are removed. For example, precautionary measures in healthcare settings (such as mandates for face coverings) have been lifted, increasing the risk for the specified population when they need to access routine monitoring or treatment. This makes timely	Thank you for your comment. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible. No action is needed.

Section	Stakeholder	Comments [sic]	Action
		access to post-exposure treatments, through timely approval processes, crucial.	
Additional comments on the draft remit		No comments	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	LUPUS UK	The background information should include data about the uptake of vaccination amongst vulnerable groups. The uptake of booster vaccinations has been decreasing for a variety of reasons. Many people are experiencing vaccine fatigue, in part because of the uncertainty around any potential added benefit from each dose. Some in our patient community have also reported that the vaccine triggers a flare of their lupus, and so they are balancing their COVID-19 risk with the vaccine making them unwell, and some do not want to keep having additional doses for this reason. For example, on our patient forum, there are mixed feelings towards having further vaccines. Users have said: • *"Every time I have a vaccine I experience a flare worse than the last. I won't have any more."* • *"I believe vaccination is important, but there is nothing for me against COVID-19 because I experience too many side effects to have any more of those. And we're told they don't work that well for people like us anyway, so what's the point. There's not much empathy for us as people just assume I'm an anti-vaxxer, but I'd love something that works without making me so ill!"* • *"Each vaccine induces a bad flare, but I will keep having them because I am high risk."*	Thank you for your comment. The background section of the scope is intended only as a brief outline of the condition and treatment pathway. No action required.

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		With an immunosuppressed cohort size for the 2023 autumn booster programme of approximately 2 million in England, the uptake numbers published by NHS England in early November 2023 puts uptake of autumn boosters among the immunosuppressed at just 14.6%. With reduced uptake of preventative vaccinations, post-exposure treatments are becoming even more important in managing the impact of COVID-19, even where vaccines may be the primary pharmaceutical intervention.	
Population	Forgotten Lives UK	yes	Thank you for your comment. No action required.
	LUPUS UK	The population group should be expanded to those at risk of severe secondary complications from infections which require hospitalisation or changes to their treatment regimens. Post-COVID syndrome is considered as an outcome in the draft scope, however this should be expanded to those who experience severe secondary complications of their existing disease or illness, which may not be classed as post-COVID syndrome. According to a LUPUS UK survey from 2022, many people with lupus, including those who are not severely immunocompromised, are hospitalised following a COVID-19 infection because of secondary complications such as pneumonia or lupus flares. This is supported by peer reviewed research which has found COVID-19 may worsen lupus symptoms (Fernandez-Ruiz, et al., 2020: https://www.translationalres.com/article/S1931-5244(20)30302-9/fulltext) and that co-morbidities such as heart disease puts people with lupus at greater risk of severe outcomes from COVID-19 (Mehta et al., 2022: https://link.springer.com/article/10.1007/s10067-022-06227-7). According to our survey, worsened lupus symptoms from lupus flares frequently required additional treatment, such as increased corticosteroids. Additionally, approximately 43% of those who responded in our survey indicated that	Thank you for your comment. NICE can only appraise a medicine within its marketing authorisation. In TA878, risk was defined using the risk criteria produced in the McInnes report, which includes people receiving treatment for immune-mediated inflammatory disorders. No action required.

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		having COVID-19 had also disrupted their normal treatment. Some people reported that they were instructed to pause their lupus medications until recovered from COVID-19 and this risked flares of their disease: • *COVID put me into a flare that lasted for four months; limiting the amount I could do and leading to severe fatigue and constant pain in my joints."* • *"COVID triggered my lupus & polymyositis - joint/muscle pain and inability to move due to excruciating joint pain. I was then put on steroids."* • *"I had to stop immunosuppressants for 3 weeks which meant a flare of some of my lupus symptoms."* • *I had to come off drugs. It caused a lupus flare."* • *"I was unable to restart medication due to having COVID and not being able to repeat bloods or be on immunosuppressant due to infection, which resulted in joint pain and swelling."* • *"Had to stop medication and felt like I was in a flare for circa 2 months despite restarting medication."* Providing post-exposure treatment to this expanded group may reduce these secondary impacts and associated costs for the NHS, such as increased lupus treatment costs and increased contacts with primary and specialist care, as well as associated wider costs such as increased absence from work or impact on caregivers.	
	Long Covid SOS	Would widen this to include those with Long Covid (post-Covid 19 syndrome) to prevent worsening of symptoms and would welcome further research into the effect into this population as one of the current theories for the cause of Long Covid is viral reservoirs	Thank you for your comment. NICE can only appraise a medicine within its marketing authorisation. No action required.

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Subgroups	Merck Sharp & Dohme (company)	Given the high proportion of patients in which nirmatrelvir plus ritonavir is contraindicated or is unsuitable for use due to clinical considerations, MSD would like to propose an additional subgroup of patients contraindicated to nirmatrelvir plus ritonavir. MSD agree with the other subgroups proposed in the draft scope, but highlight that available supporting data may use alternative definitions of high risk which may not always fully align with the McInnes definition of high risk used in TA878.[2,4] Data for specific risk factors may also be challenging to capture and could also be open to interpretation.	Thank you for your comment. The subgroups section of the scope has been updated to include people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable.
	Cardiothoracic Transplant Patient Group, NHSBT	People who have received a heart transplant People who have received a lung transplant	Thank you for your comment. People who are solid organ transplant recipients are considered in the risk factors for severe COVID-19 as described in TA878. No action required.
	Long Covid SOS	As stated above	Thank you for your comment. Please see the response made above.
Comparators	Merck Sharp & Dohme (company)	While in principle MSD agree with the suggested comparators because they capture the current treatment pathway, as suggested above, we consider it appropriate to have separate subgroup analyses based on anticipated clinical practice. For example, nirmatrelvir plus ritonavir would not be used in the	Thank you for your comment. The subgroups section of the scope has been

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		subgroup of patients contraindicated to nirmatrelvir plus ritonavir, and sotrovimab would instead be used to treat this subgroup of patients. However, MSD also acknowledge that there may be cases where there is no specific clinical justification to exclude a treatment choice. Patient preferences and logistics associated with each treatment could play a pivotal role in the treatment decision. In such scenarios, treatments could be seen as mutually exclusive for the purposes of decision making meaning that in some instances some patients may not receive any of the treatments recommended.	updated to include people for whom nirmatrelvir plus ritonavir is contraindicated or unsuitable.
	Forgotten Lives UK	yes	Thank you for your comment. No action required.
	Long Covid SOS	As far as aware	Thank you for your comment. No action required.
Outcomes	Forgotten Lives UK	yes	Thank you for your comment. No action required.
	LUPUS UK	• Outcomes should include more secondary impacts of COVID-19 to accurately capture the health and economic impact of preventing COVID-19 infections. During the Partial Rapid Review of TA878 [consultation ID6262], the medical expert raised that mortality and hospitalisations, while important, no longer fully capture the impact of COVID-19. The expert, and practicing medical professionals on the Committee, noted that the main impact on the NHS is now in primary and social care, when COVID-19 causes deterioration in existing health conditions or in health more generally. This includes people that were not hospitalised and people that do not have post-COVID-19	Thank you for your comment. It is anticipated that the outcomes time to recovery and time to return to normal activities will capture the secondary impact of COVID-19 on people

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		syndrome, so without including these secondary impacts there will be uncaptured benefits of preventing severe outcomes in any modelling. • Related to our recommendation of expanding the population that this treatment is available to, outcome measures should also consider the incidence and impact of secondary complications and chronic disease flares caused by COVID-19 infection that are not classed as post-COVID syndrome. The health-related quality of life measure needs to accurately reflect the utility gain for the recipient of the treatment, as well as for carers and/or other people in their household. This means not requiring patients to suggest they will completely stop all protective measures for there to be a utility gain. It is unrealistic to expect patients, who have needed to shield or modify their behaviour for their own safety for over three years, to immediately return to pre-pandemic behaviour, even if a treatment was able to provide 100% protection against severe outcomes, not least because patients in recent research have discussed impacts to their mental and physical health, including a loss of confidence and physical decline (e.g. Sloan et al, 2021; Ryan et al, 2022; Maldonado et al, 2021). Additionally, COVID-19 is not the only viral risk for this group, so many would have been practicing enhanced precautionary measures to reduce risk of exposure to viral and bacterial threats before the pandemic. Therefore, it is likely patients will continue to modify their behaviour in some form due to the very real need to reduce risk from infections of all kinds. In the expert patient evidence submitted by Patient Advocacy Group stakeholders and individual patients in the appraisal of Evusheld, they were not necessarily requesting a complete return to their pre-pandemic life, but a desire and need to have more of life open to them (even if that still includes some precautions like masking, for example), and that this could make huge improvements to their mental and physical health. When considering direct utility gains related to changes in shielding behaviours due to access to treatments, the committee should consider change over time as people re-gain confidence and physical strength, rather	with underlying health conditions within the population covered by the marketing authorisation. Secondary complications and chronic disease flares can be captured with tools that measure health-related quality of life. All available data for these outcomes, and the impact of behaviour on quality of life will be considered by the committee. No action required.

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		than just immediate changes in behaviour. Continuing some shielding or protective behaviours should also not be viewed as a lack of impact, as there can still be a significant impact on mental and physical health if people feel able to do more whilst still masking, for example, and some protective behaviours are likely due to increased risk from other viral or bacterial infection for this group	
	Long Covid SOS	Pleased to see that symptoms of Long Covid (post covid-19 syndrome) is an outcome measure. There is some evidence that Long Covid is prevented with molnupiravir (https://www.bmj.com/content/381/bmj-2022-074572). It would be useful to have research with the Covid-19 treatments on the prevention of worsening or relapse on long covid (post covid-19 syndrome). It may also be the case that these drugs could be a form of treatment of Long Covid itself, which is being investigated with the US trial RECOVER – vital is studying in the first line treatment https://trials.recovercovid.org/vital	Thank you for your comment. NICE can only appraise a medicine within its marketing authorisation. No action required.
Equality	Merck Sharp & Dohme (company)	MSD would like to highlight that molnupiravir offers an option for patients with protected characteristics, such as older patients or those with long-term conditions and/or disabilities, who may not currently have a viable alternative treatment option: • As an oral medication, molnupiravir provides a treatment for patients with protected characteristics who may encounter additional burden from travelling for treatment. • In addition, oral administration of molnupiravir at home would reduce exposure of patients with protected characteristics to other patients with communicable diseases in hospital or clinic settings. • Molnupiravir provides a simple alternative option for physicians treating patients with multiple comorbidities and medications, as it does not have any DDIs or require dose adjustments.	Thank you for your comment. The equalities impact assessment has been updated to include issues.

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		• Unlike alternatives, molnupiravir can be used in patients with renal impairment, the prevalence of which is higher in Black, Asian and other minority ethnic backgrounds.5 These groups also have a higher risk of death from COVID-19.6 With the addition of a subgroup of patients contraindicated for nirmatrelvir plus ritonavir, MSD do not think the draft scope will lead to exclusion, discrimination or adverse impacts on people with protected characteristics	
	LUPUS UK	In previous appraisals of prophylactic and post-infection treatments for COVID-19, there were some inaccurate assumptions made about the precautionary measures made by this patient cohort and their households. We raised these in appraisals for those treatments, and we are repeating them here as they are relevant to the accurate appraisal of Molnupiravir. The draft recommendation for the Evusheld appraisal implied that, because (some) people at higher risk from COVID-19 continue to modify their behaviour by shielding, their true risk cannot be fully considered in cost-effectiveness modelling. Section 3.16 of the draft recommendation stated that: "…data for the general population [on infection risk] may not be generalisable to those likely to have Evusheld. The committee considered it likely that the risk of infection in those eligible for Evusheld would be lower than the general population. This is because those eligible for Evusheld modify their behaviour, which remains an effective way to reduce risk of infection, despite the substantial burden." The committee then considered that the model should be sensitive to changes or differences in background levels of risk. It is unreasonable to expect people in the eligible group to continue to modify their behaviour to reduce risk of infection. Using this as evidence of a lower level of risk than the general population could mean recommendations require people to continue to shield and does not account for the large number of eligible people unable to do this.	Thank you for your comment. The equalities impact assessment has been updated to include issues around shielding.

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		The committee may also need to review any stereotypes of a person who is shielding. We cannot assume that those at risk can reduce their risk of exposure to the virus by modifying just their own behaviour. Many in the at-risk group do not live alone. It is more likely that someone is in a household with family or friends whose behaviour would also need to be modified. This becomes increasingly difficult due to the lack of precautionary measures and governmental support, such as widespread testing. We must also consider the reduced opportunities for at-risk people to practice shielding. Most people in this group are living with a disease and/or treatment which requires attendance to medical settings for medication administration and/or monitoring. Even if an at-risk person can stay safe traveling to and from appointments, the precautionary measures in medical settings are being increasingly abandoned. It is not reasonable to use lower risk values to model cost-effectiveness for this group, because it is not reasonable to assume that all at-risk people and their households are able to adequately modify their behaviour, nor is it reasonable to expect those that are able to, to continue shielding given the difficulties and well-documented mental and physical health impacts of this (e.g. Sloan et al, 2021; Ryan et al, 2022; Maldonado et al, 2021). This is also a matter of health inequalities. A disproportionate number of those unable to shield are from minority ethnic groups, due to the higher likelihood that they are in employment without remote working options, higher likelihood to work in occupations with higher risk of exposure to COVID-19, and higher likelihood of needing to use public transport to travel to work (POST, 2020). Lupus also disproportionately affects those from African-Caribbean or Asian heritage, who also tend to have more severe disease (e.g. Hasan et al, 2022), and so would likely be a high proportion of those eligible for Molnupiravir.	
Other considerations	LUPUS UK	Access to COVID-19 treatments for people who have tested positive has been disrupted by the change in access pathways from one national to many different local systems. Many eligible patients (and their healthcare providers)	Thank you for your comment. Evidence

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		do not know who to contact when they require post-exposure treatment, and this has led to delays in access to treatments which must be given within a short window.	provided with regards to access to treatment will be considered by the committee. No action required.
Questions for consultation	Merck Sharp & Dohme (company)	• *Where do you consider molnupiravir will fit into the existing care pathway for COVID-19?* MSD consider that molnupiravir would be used to treat patients with mild to moderate COVID-19 at risk of developing severe disease. This would include patients with risk factors such as respiratory, renal or liver disease, neurological disorders, Down's syndrome, cancer, haematological disease, HIV/AIDS or immune deficiencies. Risk factors could also include age, BMI, heart disease and/or diabetes. Molnupiravir would also be used to treat patients with contraindications to nirmatrelvir plus ritonavir and who express a preference for an oral treatment or for whom it is not feasible to receive sotrovimab intravenous infusion in the outpatient setting, for example inability to travel. • *What technologies are established clinical management?* Current clinical management of patients with mild to moderate COVID-19 at risk of developing severe disease consists of either nirmatrelvir plus ritonavir; or sotrovimab for patients in whom nirmatrelvir plus ritonavir is contraindicated. • *Would molnupiravir be a candidate for managed access?* [redacted] • *Do you consider that the use of molnupiravir can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you*	Thank you for your comment.

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		understand to be available to enable the committee to take account of these benefits. MSD consider that, for the purposes of the decision problem, the QALY framework is adequate. However, it does not necessarily capture wider health-related benefits that could materialise from having an alternative treatment option to treat patients at high risk of developing severe disease and contraindicated for other treatment options. For example, these high-risk patients and their carers may be at increased risk of mental health issues as a result of social isolation and health anxiety, and fear of contagion. Molnupiravir could alleviate these issues by offering high-risk patients a treatment option to be able to re-engage in social interactions more quickly and reduce health concerns. There are also potential long-term consequences that cannot be fully quantified within the current QALY framework due to limited data as a result of the rare frequency of occurrence. An example of this is the potential harm caused by the suboptimal management of emergent DDIs which can range in resolution and health impact from a few days with minimal disutility to long-term with large overall disutility. To enable the Committee to fully take these benefits into account, it is important to review the literature for publications reporting the frequency of DDIs alongside clinical opinion on long term effects. Other considerations that fall outside the strict patient QALY framework used for decision making by NICE, but are important for specific individuals, include the indirect workforce impact that COVID-19 can have on social and health care services, with control of infection rates resulting in a positive impact on vulnerable individuals. This would be expected to have a positive impact for the NHS and the society overall. • *What additional COVID-19 NHS testing costs (if any) need to be considered for people who might be eligible for treatment with molnupiravir?*	The committee will consider the availability of current treatments for COVID-19. The committee will consider evidence on impacts to health related quality of life. Wider societal benefits would not be included in the appraisal. The NICE health technology evaluation manual states that *"…in exceptional circumstances for medicines, when requested by the*

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		Molnupiravir treatment would not require additional testing compared to currently available treatments.	*Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* The aim of an evaluation of treatments for COVID-19 is to inform the management of COVID-19 as it becomes a routine part of NHS work, rather than an exceptional circumstance.
	Long Covid SOS	Does the economic modelling capture the impact beyond the severe cases that end up in hospital to cases that subsequently develop Long Covid in the community (attendance at outpatient clinics, primary care, inability to be economically active, carry out caring responsibilities etc)?	Thank you for your comment. The symptoms of post-COVID-19 syndrome (also known as long COVID) are included in the outcome measures. Wider societal benefits would not be included in the appraisal. The NICE health technology evaluation manual

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			states that *"…in exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* The aim of an evaluation of treatments for COVID-19 is to inform the management of COVID-19 as it becomes a routine part of NHS work, rather than an exceptional circumstance. The NICE health technology evaluation manual states that *"Productivity costs should be excluded from the reference case."* No action required.

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Additional comments on the draft scope		No comments	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

GSK UK