Peer review comments – Antivirals [Remdesivir + Molnupiravir]

Managing COVID-19 rapid guideline (NG191)

Peer review organisations

For a list of stakeholders invited to comment on COVID-19 guidance as part of the targeted peer review, please see the targeted peer review stakeholder list on the NICE website.

For this topic, the following stakeholder organisation was also invited to comment:

- Royal College of Pathologists

Overarching category	Guideline section	Theme of comments	Action taken
General comments	Recommendation + research recommendation – Combination therapy [antivirals / nMAbs]	Some reviewers expressed concern about the appropriateness of the consensus recommendation to not routinely offer combination treatment except as part of a clinical trial. Reviewers argued that there is evidence and clinical experience for the use and benefit of combination treatment for some groups of hospitalised people e.g people who are antibody deficient, and the urgent need for optimal treatment for these people. Reviewers also pointed out the difficulties of running clinical trials to evaluate the risks or benefits of combination therapies in this population due to ethical concerns as well as small study populations.A few case reports and case series	The consensus recommendation for combination treatment has been removed. This has been replaced with an additional section in the Evidence to Decision sections for both the remdesivir and molnupiravir recommendations to reference the panel's discussion around combination treatment. There is also a research recommendation to investigate the potential benefits and harms of combination treatment in people who do not need supplemental oxygen for COVID-19 and who are at high risk of progression to severe disease.

Date of completion: xx/xx/xxxx

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		were referenced to strengthen the justification of use of combination therapy in clinical use.	Additional clarification was made to the existing research recommendation on combination treatment to include a subgroup of people who are at risk of not mounting an immune response.
General comments	Recommendation - Remdesivir	Reviewers highlighted the ommission of young people aged 12-17 in the remdesivir recommendation.	The recommendation was modified to include “young people aged 12 years and over and weighing 40 kg or more”, and a remark was added to indicate that remdesivir use is currently off-label in this group. Revisions were also made to the rationale and Evidence to Decision sections.
Clarifications	Recommendations – Remdesivir + Molnupiravir	A reviewer clarified that the terminology used in the national commissioning policy is ‘highest risk’ and not ‘high risk’. Another reviewer highlighted differences in the definitions of ‘high risk’ in the national commissioning policy and the inclusion criteria of the MOVe-OUT and PINETREE studies, and queried whether the guidelines should state more explicitly the differences in the patient inclusion criteria. The reviewer also queried if the following statement requires more information and context. ‘When assessing the person, take into account their vaccination status…”.’	The reference to the commissioning policy has been modified to state that it ‘provides a list of people who have been prioritised for treatment with antivirals.’ We have ensured that risk factors for the study populations are stated in the Evidence to Decision section. We clarified that clinicans should consider the person’s likely response to any vaccinations already given in their decision-making around antivirals. Clinical advisers felt that clinicans would understand that vaccinated patients are at lower risk of progression to severe disease, but wanted to ensure that clinicians would also consider that people who are immunosuppressed may not be able to mount an antibody response to vaccination.

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			A link to the interim national commissioning policy is included in the recommendations section to indicate access to treatment for molnupiravir and remdesivir in the UK.
Clarifications	Evidence Summaries – Molnupiravir + Remdesivir	Reviewers pointed out that recommendations are based on the evidence which included only 'unvaccinated' people, that might impact the direct relevance of the evidence to the UK population. Therefore, it has been suggested that indirectness of the evidence should be explicitly mentioned.	The 'Summary' section of the evidence profile has been updated for both molnupiravir and remdesivir to emphasise that the results are based on unvaccinated study populations. This has also been updated in the certainty of the evidence sections and plain text summaries in the GRADE tables. All outcomes were downgraded at an earlier point for indirectness due to the study populations being unvaccinated.
Clarificiations	Recommendations – Molnupiravir + Remdesivir	One reviewer highlighted that the national commissioning policy does not include any consideration of vaccination status, while NICE guidelines states that vaccination status should be considered while assessing the patient.	The panel considered that a person's likely response to vaccination is an important factor in determining risk of progression to severe COVID-19 and important for clinicians to take into account when assessing a patient. Clinical advisers felt that clinicans would understand that vaccinated patients are at lower risk of progression to severe disease, but wanted to ensure that clinicians would also consider that people who are immunosuppressed may not be able to mount an antibody response to vaccination.

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Modifications	Research recommendations	A reviewer highlighted the importance of the following factors on the effectiveness and safety of antiviral therapies: - Pregnancy - Serostatus - Ethnicity - Age - Variant They were also interested in understanding: - Factors influencing disparities in access to/treatment with antivirals - Reasons for disparities in access to antivirals	The research recommendation investigating the effectiveness and safety of remdesivir in vaccinated people includes pregnant women, ethnic minorities, COVID variants, and seropositive people as subgroups of particular interest. Other research suggestions around drivers of access disparities were not included as they did not arise from panel discussion.
Clarifications	Evidence to Decision – Remdesivir	One reviewer asked for clarification to be added that people in the PINETREE trial had normal blood tests at baseline, as this may impact safety outcomes.	Clarification has been added to the Evidence to Decision for the remdesivir recommendation and to the Summary section of the evidence profile for remdesivir.
Clarifications	Evidence to Decision – Remdesivir	One reviewer pointed out that ethnic minority subgroups were underrepresented in the the PINETREE study.	Minor amendments have been made to the Evidence to Decision for the remdesivir recommendation to highlight that the PINETREE study underrepresented ethnic minority groups.
Clarifications	Evidence to Decision – Remdesivir	Some reviewers pointed out that patient transport is provided for those with COVID-19 to attend infusion appointments, but noted that patient transport schemes may be difficult to access.	Additional detail around patient transport schemes has been added to the Evidence to Decision for the remdesivir recommendation.

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General comments	Evidence to Decision – Remdesivir	One reviewer emphasised that messaging around antiviral treatment options needs to be culturally competent to cater for ethnic minorities, people with learning disabilities, people with language barriers and people who are visually impaired.	No action was taken as advising on messaging is not within the scope of this review and subsequent recommendations, and the panel did not raise concerns about messaging during the meeting.
General comments	Evidence to Decision – Remdesivir	One reviewer noted that people with lower socioeconomic status, those from ethnic minoritiy groups, people living with homelessness or people from traveller communities could find treatment with remdesivir inaccessible due to: - Lack of treatment awareness - Inability to travel to and from an infusion site - Inability to visit an infusion site for 3 consecutive days - Limited access to GP	The Equity section of the Evidence to Decision for the remdesivir recommendation has been amended to include these potential barriers to access.
General comments	Evidence to Decision – Remdesivir	One reviewer noted that, while COVID-19 Medicine Delivery Units (CMDUs) are used in England, the devolved administrations may have different options for supplying COVID-19 medicines.	Clarification has been added to the Evidence to Decision for the remdesivir recommendation.
General comments	Evidence to Decision – Remdesivir	One reviewer suggested that NHS trusts may struggle to accommodate remdesivir infusions	No action was taken as the panel's concerns around the feasibility of remdesivir infusions have already been included in the 'Feasibility' section of

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			the Evidence to Decision of the remdesivir recommendation.
General comments	Evidence to Decision – Remdesivir	One reviewer indicated that additional evidence around the effectiveness of remdesivir would be helpful, particularly in light of vaccination rates in the UK.	No action was taken. The panel have drafted a research recommendation to investigate the effectiveness and safety of remdesivir in vaccinated people.
General comments	Recommendation – Remdesivir	One reviewer suggested that the NHS England Interim Clinical Commissioning Policy should instead be referred to as a UK-wide policy.	No action was taken. The NICE guideline covers England and so the recommendations are written for that primary audience. Therefore, this has not been included in the content to avoid confusion. This also maintains consistency with other recommendations. The policy makes it clear that it is UK wide.
General comments	Recommendation + Evidence to Decision – Molnupiravir	A reviewer highlighted differences in outcomes based on antibody status, as the results were more favourable for people with seronegative status at baseline vs people with seronegative status. Another reviewer queried whether there should be a reduced recommendation if serostatus is known to be positive.	No action was taken as the panel's discussion about serostatus is already included in the Evidence to Decision for the molnupiravir recommendation. The evidence was not considered sufficient to include differential recommendations based on serostatus. The seropositive group comprised of smaller number of people and (events/total; 5/136 in the molnupiravir group, 2/146 in placebo group) compared to the seronegative group (39/541 in molnupiravir and 64/541 in placebo). In the second trial (Fischer 2021), the number of people with positive antibody status was also not enough to draft recommendations with high certainty.

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General Comments	Recommendations Molnupiravir	One reviewer had no specific concerns with the guidance but pointed out that recommendations are based on trials in unvaccinated people prior to the emergence of Omicron variant and conducted outside the UK, and also considered that the recommendations were likely to impact recruitment into the PANORAMIC study.	No action was required. Information related to these points is included in the remark section below the recommendation. There is also a link to the eligibility criteria for PANORAMIC.
General Comment	Recommendations Molnupiravir	One reviewer commented that it might be useful to indicate molnupiravir for those who cannot access intravenous – remdesivir therapy.	No action was required. NICE has not conducted a comparative analysis between different antivirals to inform such a recommendation.
Clarifications	Recommendation – Molnupiravir Evidence to Decision	One reviewer highlighted that published results from the MOVe-OUT trial were for people who had symptom-onset within 5 days of treatment initiation, while the study protocol indicated within 7 days.	Minor amendments have been made to the evidence summary to make clear that the published results are for people who had symptom-onset within 5 days of treatment initiation.
Modifications	Recommendation – Molnupiravir Evidence to Decision - Equity	One reviewer highlighted challenges in terms of accessing the medicine if travel is needed and also highlighted benefits associated with home delivery.	Updated with minor amendements to the Equity section of the Evidence to Decision to reflect this.
Clarifications	Recommendation – Molnupiravir –	One reviewer asked if there are any concerns for paternal exposure of molnupiravir in terms of	Please see the Summary of Product characteristics for information related to fertility. A

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	Evidence to Decision – Benefits and Harms	fertility, and whether additional precautions are needed.	link to the SmPC has also been added to the guideline.