Peer review comments – Nirmatrelvir and ritonavir (Paxlovid)

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.

Peer review comments

Overarching category	Guideline section	Theme of comments	Action taken
Info box	Info box	[No comments]	[No actions taken]
Nirmatrelvir and ritonavir recommendation and evidence to decision section	Recommendation and certainty of the evidence	One reviewer suggested that we should consider studies for vaccinated people who are at high risk.	Thank you for your comment. The EPIC-HR study (Hammond 2022) is currently the only published RCT. When the following ongoing studies have published, we will include them in the evidence review: PANORAMIC and EPIC-SR as these should provide more direct evidence on the effectiveness of nirmatrelvir and ritonavir in vaccinated adults at high risk with COVID-19. EPIC-Peds should provide evidence on the effectiveness of nirmatrelvir and ritonavir in children with COVID-19.
Nirmatrelvir and ritonavir recommendation	Recommendation	One reviewer suggested that we should add a bullet-point to the recommendation on the need to consider contraindications associated with	Thank you for your comment. We have included advice on nirmatrelvir and ritonavir's contraindications and the need for a full medication review in the remark section just below

Date of completion: 29/03/2022

Overarching category	Guideline section	Theme of comments	Action taken
		Nirmatrelvir and ritonavir and a person's medication history.	the recommendation. The remark section will always be visible.
Nirmatrelvir and ritonavir recommendation	Recommendation	One reviewer suggested that we should include a consideration of symptoms, or lack of, when assessing the person.	Thank you for your comment. The recommendation makes clear that one of the factors to take into account when assessing the person is whether their condition is deteriorating, which encapsulates whether or not the person has symptoms.
Nirmatrelvir and ritonavir recommendation	Recommendation	One reviewer highlighted the lack of trial evidence in vaccinated populations with Omicon and considered that the people most likely to benefit would be in those for whom the impact of vaccination is likely to have been significantly reduced by immunosuppression (based on cohort studies), or patients who have not been vaccinated.	Thank you for your comments. The recommendation highlights the need to take into account a person's likely response to any vaccinations already given. The limitations in the evidence base, in particular the lack of trial evidence in vaccinated populations with Omicon, are covered in the Evidence to Decision section.
Nirmatrelvir and ritonavir recommendation and Evidence to decision section	Remark section and Drug interactions section	One reviewer suggested that we should use the term "medication history" rather than "medication review".	Thank you for your comment. The term "medication history" might be misinterpreted as meaning medications that the person has taken in the past. Therefore, we have used the word "review".
Nirmatrelvir and ritonavir recommendation	Remark	One reviewer suggested that we should include a summary of results to facilitate shared decision-making.	Thank you for your comment. When recommendations are published in MAGICapp, there is a feature on the MAGICapp website that automatically creates decision aids. These decision aids include graphical representations of the results. These visual aids should be more helpful than written or numerical descriptions.
Evidence to decision section	Benefits and harms	One reviewer suggested that we should mention that the study took place at a time when the Omicon variant was not prevalent.	Thank you for your comment. This is included in the recommendation section in the remark, and in the 'Evidence to Decision' section under 'Certainty of the Evidence'.

Overarching category	Guideline section	Theme of comments	Action taken
Evidence to decision section	Benefits and harms	One reviewer suggested that, in the addition to the number of deaths in each arm, we should include the total number of patients.	Thank you for your comment. We have now added this information.
Evidence to decision section	Benefits and harms	One reviewer suggested that we should include common adverse events in the benefits and harms section.	Thank you for your comment. We have now added this information in the section on adverse events.
Evidence to decision section	Drug interactions	Two reviewers agreed with our advice that a full medication review should be undertaken.	Thank you for your comments.
Evidence to decision section	Drug interactions	One reviewer suggested that we should include a hyperlink to the Specialist Pharmacy Service advice as well as to the summary of product characteristics.	Thank you for your comment. The summary of product characteristics is a primary source of information for safety, while the Specialist Pharmacy Service (SPS) is secondary (although for many topics their advice is more accessible for busy pharmacists). We note that the SPS site says "This list is not comprehensive. If a medicine is not listed also check University of Liverpool COVID-19 Drug Interaction checker (https://covid19-druginteractions.org/checker)". We also link to the Liverpool site for interactions (which is appropriate because there are so many).
Evidence to decision section	Certainty of the evidence	One reviewer highlighted that the EPIC-HR trial included a very low number of people who were immunosuppressed or who had cancer whereas these groups of people comprise the majority of people who are offered nirmatrelvir and ritonavir in the UK.	Thank you for your comment. We have included a sentence noting the low representation in the trial of some high-risk groups, including people with cancer and people who were immunosuppressed and the difficulties this poses in drawing conclusions.
Evidence to decision section	Certainty of the evidence	One reviewer suggested that we should delete the outcomes: death from any cause, and hospitalisation for COVID-19.	Thank you for your comment. We have kept these outcomes because they are different from the composite outcome of hospitalisation for COVID-19 or death from any cause. However, we have clarified this in the text..
Evidence to decision section	Certainty of the evidence	One reviewer suggested that there are statistically significant differences in the degree	Thank you for your comment. In our subgroup analyses using RevMan, the I^2 statistic for

Overarching category	Guideline section	Theme of comments	Action taken
		of improvement by age group and by baseline serology status where confidence intervals do not overlap between subgroups.	heterogeneity never exceeded 17% for any subgroup analysis, which is low heterogeneity. By contrast, an I^2 statistic of more than 50% is considered to be high with regards to heterogeneity. These results do not indicate a difference between any of the subgroups in the risk ratios for the primary outcome.
Evidence to decision section	Equity	One reviewer agreed with the sentence: The panel noted that the ability to access nirmatrelvir and ritonavir in the community may benefit people who have limited access to healthcare facilities as it can be delivered to their home. However, they suggested that we should add: "…compared to other treatments that are administered in a healthcare facility."	Thank you for your comment. As there are other oral treatments available for the population being considered, such as molnupiravir, we have not changed this sentence.
Evidence to decision section	Equity	One reviewer agreed that nirmatrelvir and ritonavir is unlikely to be recommended in pregnancy and is supportive of the wording as it stands.	Thank you for your comment.
PICO	Description of the PICO	With reference to this sentence: "People with COVID-19 and symptom onset in the last 7 days" One reviewer suggested that we should change "7 days" to "5 days".	Thank you for your comment. Our PICO includes people with COVID-19 with symptom onset in the last 7 days. However, the EPIC-HR study and the NICE recommendation based on this evidence, only includes people who have symptom onset in the last 5 days.