NICE National Institute for Health and Care Excellence

Tixagevimab plus cilgavimab for preventing COVID-19 [ID6136]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on **Thursday 9 March 2023**. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	LUPUS UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Debbie Kinsey

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Evusheld was effective and cost-effective, and therefore likely to have been approved, when previous Omicron variants were more dominant. It is both frustrating and concerning that an opportunity was missed to address an urgent unmet need for people who are at high risk from COVID-19, particularly those who do not have a good response to, or are unable to receive, vaccinations. If Evusheld had been appraised more rapidly, these vulnerable patients may have been able to have some protection from COVID-19 when previous variants were dominant during the second half of 2022. In addition to providing vital protection by reducing risk of severe illness, this treatment could have drastically improved quality of life for a group of people continuing to experience the adverse impact of shielding. We welcome the recommendation to create a new fast-track system for updating recommendations for COVID-19 treatments, particularly in the case of monoclonal antibodies which are most effective against particular variants. However, as we understand it, this process is for *updating* existing recommendations, and not for the evaluation of *new* treatments. This means potential future prophylaxis preventative treatments will not be included. Therefore, the rapid review scheme will not solve the problem of appraising novel treatments in a timely manner. It is essential that new and novel COVID-19 treatments are included in a fast-track system, so that another effective treatment is not wasted due to the appraisal process taking place after the window of opportunity for its effective use is passed.
2	We are concerned that the recommendations imply that NICE requires a threshold of evidence which is too high for medicines such as these to be approved in a timely manner. In section 3.23, the committee recommends that "further data collection through clinical trial would be a more appropriate way to resolve key uncertainties". Given the long timescales of clinical trials, and the issues of changes in circulating variants, waiting for the outcome of a clinical trial will likely delay appraisal to a point at which the variants have changed and the treatment becomes less effective (as discussed above). The reliance on in-vitro evidence alone is problematic, as this approach makes significant assumptions regarding tissue penetration and mechanism of action of monoclonal antibodies, as research has indicated that in-vitro studies analysing the neutralising effect of monoclonal antibodies on different variants of SARS-Cov-2 do not accurately demonstrate the real-world, clinical efficacy of treatments. In some cases a monoclonal antibody developed for a historic variant could regain activity against the spike protein of a future variant. As such, the recommendations should not be reliant on in-vitro analyses. Uraki et al. (2022) demonstrated that another monoclonal antibody treatment, sotrovimab, can restrict viral replication in the lungs of hamsters infected with Omicron BA.2 in an in-vivo experiment, despite in-vitro experiments suggesting that Omicron BA.2 had resistance to sotrovimab. The threshold of evidence to enter a COVID-19 treatment into clinical practice is unrealistically high, especially due to the rapid changes in circulating variants. On the other hand, the threshold to withhold or withdraw the same treatment is much lower when based on in-vitro neutralising evidence alone. This disproportionately affects people at higher risk of COVID-19 whose medications or comorbidities mean they have little response to, or are unable to receive, vaccination. A wider range of evidence needs to be synthesised for rapid and accurate assessment of the efficacy of monoclonal antibody treatments.

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3	We are concerned that evidence used by the committee for this recommendation implies 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 recommendations states 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. The committee may 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 unlikely 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 Evusheld.
4	We are concerned that the committee has underestimated the direct utility gain to shielding patients. The committee suggests that the evidence submitted by patient experts implies a lower direct utility gain due to more limited behaviour change in shielding behaviours than the Company submitted in evidence. It is unrealistic to expect patients, who have needed to shield or modify their behaviour for their own safety for almost three years, to immediately return to pre-pandemic behaviour, even if a treatment was able to provide 100% protection. Patients in recent research (as referenced in point 3 above) have discussed impacts to their mental and physical health, including a loss of confidence and physical decline. Given these impacts, it is unrealistic to expect these patients to immediately or fully return to pre-pandemic behaviours. 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.

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	Additionally, in the expert patient evidence submitted by Patient Advocacy Group stakeholders and individual patients, patients 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, the committee should consider change over time as people re-gain confidence and physical strength, rather 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.
5	We are concerned that the recommendations do not include or imply a defined threshold of accepted effectiveness. The landscape of the pandemic has changed dramatically since the clinical trials for Evusheld. We are no longer experiencing a single dominant variant in circulation at one time but instead there are several dominant variants. It is unclear how this could change in the future, but it may not return to a pattern of single variants at a time. Monoclonal antibodies such as Evusheld usually work most effectively against one particular variant. As there will be more than one variant circulating, it is imperative that NICE develops a definition for the threshold of effectiveness to support rapid appraisal and deployment of effective treatments. This must include a threshold related to the estimated prevalence of variants the monoclonal antibody is likely to be effective at neutralising. If a monoclonal antibody is appraised to be effective (and cost-effective) against particular variants (such as is the case with Evusheld), then a threshold must be set for it being appraised as effective and cost-effective in the context of there always being multiple variants in circulation (for example, the FDA have accepted a threshold of using a monoclonal preventative treatment if the variant it works against is estimated to be responsible for greater than 10% of cases; FDA, 2023). Setting a clearly defined threshold will support rapid and transparent appraisal and updating of recommendations as variants change within the UK.
	References: - FDA (26th January 2023). Emergency use update open letter to AstraZeneca. https://www.fda.gov/media/154704/download - Hasan, B., Fike, A., & Hasni, S. (2022). Health disparities in systemic lupus erythematosus – a narrative review. *Clinical Rheumatology, 41(11)*, 3299-3311 - Maldonado et al (2021). Association of medication access difficulty and COVID-19-related distress with disease flares in rheumatology patients during the COVID-19 pandemic. *Arthritis Care & Research, 73(8)*, 1162-1170 - POST (2020). Impact of COVID-19 on different ethnic minority groups. Rapid response report. https://post.parliament.uk/impact-of-covid-19-on-different-ethnic-minority-groups - Ryan et al (2022). Exploring the physical, psychological and social well-being of people with rheumatoid arthritis during the coronavirus pandemic: a single-centre, longitudinal, qualitative interview study in the UK. *BMJ Open, 12(7)*, e056555 - Sloan et al (2021). COVID-19 and shielding: experiences of UK patients with lupus and related diseases. *Rheumatology advances in practice, 5(1)*, rkab003

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	- Uraki, R., Kiso, M., Iida, S., Imai, M., Takashita, E., Kuroda, M., ... & Kawaoka, Y. (2022). Characterization and antiviral susceptibility of SARS-CoV-2 Omicron BA. 2. *Nature*, *607*(7917), 119-127.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.