Peer review comments – *Casirivimab and Imdevimab - hospital use*

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 organisations were also invited to comment:

- British Thoracic Society
- Royal College of Pathologists

Overarching category	Guideline section	Theme of comments	Action taken
General comments	-	Several reviewers suggested editing grammatical/structural errors.	All grammatical/structural errors were corrected.
General comments	-	Two reviewers suggested that the communicating authors for the RECOVERY trial were Horby and Landray	All reference to Horby was updated to include Landray as they are both communicating authors.

Date of completion: 30/9/2021

Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative.	Recommendation 1	Several reviewers agreed to the content of this recommendation	No action needed.
Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative	Recommendation 1	Three reviewers highlighted that “all hospitalised patients with COVID-19” is a broad statement and there could be a clearer definition of which hospitalised groups should receive treatment.	NG191 sets out treatment recommendations for patients with confirmed COVID-19. This recommendation cannot comment on which specific groups should receive this treatment as there is insufficient evidence to support further stratification at the moment.
Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative	Recommendation 1	Several reviewers highlighted that there have been cases of clinical benefit in patients who received mAbs earlier in COVID-19 infection and those who were at a less severe disease state (e.g. receiving non-invasive ventilation).	The panel were presented evidence from the trial that showed benefit in those treated within 7 days of symptom onset and those receiving simple oxygen. However, this indication came from one trial and the panel felt that there was not enough evidence to support stratifying treatment for select groups.
Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative.	Recommendation 1	Several reviewers commented on practicalities of offering treatment, including when to sample disease, when to offer	The practicalities of serological testing were discussed at the panel meeting. NHSE have commented that practical roll out and

Date of completion: 30/9/2021

		treatment, antibody status and what type of test to use to detect infection/guide treatment (anti-NP, anti-S, anti-RBD) and how different antibody tests and assay cut-offs compare.	considerations of aspects of serological testing are being addressed. Our recommendation is based on the methods in the Horby and Landry trial, until further evidence emerges. Ultimately, these recommendations serve as guidance, and it is at the clinician's discretion to practice safe clinical judgement.
Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative.	Recommendation 1	Three reviewers indicated that further text to support the fact that treatment should only be offered to those with PCR proven COVID-19 infection, due to cases of suspected COVID-19 presenting as PCR negative and an increase in influenza/RSV which would present similar clinical signs.	NG191 covers treatment of those with confirmed COVID-19 infection and thus this recommendation aligns with that. These patients would receive PCR testing at point of care to confirm diagnosis.
Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative.	Evidence to decision – Benefits and harms	One reviewer commented that there was a discrepancy between eligibility of treatment groups in NICE recommendation (all patients hospitalised with COVID-19 aged 12 and over) and clinical commissioning policy (>=50	NICE's rec is based on the evidence from one study, and the evidence did not facilitate further stratification beyond seronegative. We note that the clinical commissioning has considered other factors to guide the policy.

Date of completion: 30/9/2021

		years old or <50 and immunocompromised).	
Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative.	Evidence to decision – Benefits and harms	Two reviewers suggested that there is emerging evidence that indicates that concomitant therapy with IL6 blockers alongside mAbs is of significant clinical benefit. The reviewers commented that despite patients enrolled in this RECOVERY trial receiving IL6 blockade and mAbs, the degree of benefit and effect of each therapy cannot be evaluated.	This has been brought to our attention by a panel member, however, as the reviewers stated we cannot evaluate the full effects of the best combination therapies to use and the effect of each therapy in isolation. As such, we can only comment on reported data and will keep this area under review as further evidence emerges.
Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative.	Evidence to decision – Benefits and harms	Several reviewers commented on the logistics and availability of serological testing across the UK and made note of possible disparities in treatment due to test availability and possible effects in delay of treatment.	The practicalities of serological testing were discussed at the panel meeting. NHSE have commented that practical roll out and considerations of aspects of serological testing are being addressed. We note possible equity issues that could arise from availability and potential delays in offering this treatment.

Date of completion: 30/9/2021

Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who are seronegative.	Evidence to decision – Benefits and harms	One reviewer commented that the drafting surrounding patients with unknown serostatus could be clarified as some data from unknown serostatus patients was reported.	Only partial data was reported in the pre-print of the trial. Once a peer reviewed manuscript is published, we will review the data reported and evaluate for impact.
Do not offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19: • Who are seropositive or; • Whose serostatus is unknown	Recommendation 2	Several reviewers agreed with the content of this section.	No action needed.
Do not offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19: • Who are seropositive or; • Whose serostatus is unknown	Recommendation 2	One reviewer suggested that the format in which the recommendation is presented can be interpreted as a "double negative" recommendation with the "Not recommended" label.	No action needed. The Not recommended label is a built-in tool in MAGICapp and follows the style of previous recommendations with a negative signal. MAGICapp has various help buttons and tools to guide users.
Do not offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19: • Who are seropositive or; • Whose serostatus is unknown	Evidence to decision – Benefits and harms	Two reviewers suggested that it is important to note the practicality issues of the 8g dosage used in the study. The reviewers cited that the CMO advocated for lower dosage of casirivimab and imdevimab (1.2g – 4.5g). The reviewers	We have signposted to the clinical commissioning policy for dosage. The panel acknowledged the lack of evidence in certain populations and dosing, and these are captured in a research recommendation.

Date of completion: 30/9/2021

		also noted the fact that there is a lack of evidence surrounding treatment benefit in immunocompromised or vaccinated individuals.	
Do not offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19: • Who are seropositive or; • Whose serostatus is unknown	Evidence to decision – Benefits and harms	Two reviewers suggested that based on this study, there is a noticeable limitation surrounding use of this treatment in immunocompromised or vaccinated individuals. They noted that there is an assumption that the effect of treatment in these groups will be the same.	These considerations are captured in our research recommendations. The panel noted that this was not reported by the trial and constitutes an important area of research.
Do not offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19: • Who are seropositive or; • Whose serostatus is unknown	Evidence to decision – Benefits and harms	One reviewer has noted that partial reporting of adverse event data is an important aspect to consider regarding safety.	No action needed.
What is the effectiveness, cost effectiveness and safety of the combination of casirivimab and imdevimab for treating COVID-19?	Research Recommendation	One reviewer suggested that it would not be justifiable to give this therapy to further	The research recommendation aims at generating, a research protocol intended to explore and ascertain effectiveness of treatment in different people, under different comparators.

Date of completion: 30/9/2021

Does effectiveness vary for people with different clinical characteristics (for example, seropositive, unknown serostatus, immunocompromised, receiving concomitant therapy)? Suggested PICO (Population, Intervention, Comparator, Outcome) P: hospitalised people with COVID-19 I: treatment with different doses of casirivimab and imdevimab C: • treatment dose with different doses • standard care against treatment dose and/or different doses • treatment in people with different clinical characteristics (for example, seropositive, unknown serostatus, immunocompromised, receiving concomitant therapy) O: • mortality		seropositive patients who have been shown to not benefit.	It was noted that evidence of lack of effect in seropositive people is from one trial and further evidence is needed to conclusively determine this consideration.

Date of completion: 30/9/2021

• progression to invasive mechanical ventilation • progression to non-invasive respiratory support • duration of hospitalisation • adverse events • costs of treatment • health-related quality of life			
What is the effectiveness, cost effectiveness and safety of the combination of casirivimab and imdevimab for treating COVID-19? Does effectiveness vary for people with different clinical characteristics (for example, seropositive, unknown serostatus, immunocompromised, receiving concomitant therapy)? Suggested PICO (Population, Intervention, Comparator, Outcome) P: hospitalised people with COVID-19 I: treatment with different doses of casirivimab and imdevimab	Research recommendation	One reviewer suggested that we should include further patient characteristics for exploration such as seropositive at different antibody levels, classes, and types. As well as a consideration of seronegative vaccine recipients.	No action needed. The research rec outlines some patient characteristics that can be considered and highlighted overarching categories, which investigators can then determine or act on further.

Date of completion: 30/9/2021

C: • treatment dose with different doses • standard care against treatment dose and/or different doses • treatment in people with different clinical characteristics (for example, seropositive, unknown serostatus, immunocompromised, receiving concomitant therapy) O: • mortality • progression to invasive mechanical ventilation • progression to non-invasive respiratory support • duration of hospitalisation • adverse events • costs of treatment • health-related quality of life			

Date of completion: 30/9/2021