

## In brief

### Monoclonal antibodies

13 December 2021

### Summary

- [Monoclonal antibodies](#) are laboratory-made proteins that mimic or enhance the human immune system response to fight against harmful antigens such as viruses. Monoclonal antibodies that can specifically [target surface viral proteins](#) to block the viral entry to host cells can be used for preventing and treating COVID-19.<sup>1, 2</sup>
- Published guidelines generally recommend:
  - casirivimab plus imdevimab in seronegative patients hospitalised with moderate to critical COVID-19 at risk of progression
  - sotrovimab for people who do not require oxygen and are at risk of progression.
  - IL-6 receptor blockers (tocilizumab or sarilumab) for treating patients with severe disease.
- A Cochrane review (updated in September 2021) concluded that there was insufficient evidence regarding the effectiveness of treatment with monoclonal antibodies.
- In terms of resistance, the neutralising effect of monoclonal antibodies can be affected by the mutations in the spike protein of the SARS-CoV-2 virus in emerging variants. There are investigations into identifying monoclonal antibodies that have broad cross-neutralising potency against variants of SARS-CoV-2 virus and less susceptibility to viral escape.

### Regulatory approvals

- In Australia, the Therapeutic Goods Administration (TGA) has provisionally approved [sotrovimab](#), [tixagevimab and cilgavimab \(Evusheld\)](#) and [casirivimab+imdevimab \(Ronapreve\)](#).<sup>3-5</sup>
- The US Food and Drug Administration (FDA) have granted Emergency Use Authorizations to three monoclonal antibodies: [casirivimab plus imdevimab](#), [sotrovimab](#), and [bamlanivimab and etesevimab](#), administered together for the treatment of mild to moderate COVID-19 in nonhospitalised patients at high risk of progression. The FDA revoked the Emergency Use Authorization for [bamlanivimab](#) when administered alone. This was initially granted authorisation in November 2020.<sup>6-9</sup>
- The FDA has also authorised [REGEN-COV](#) for emergency use as post-exposure prophylaxis (prevention) for COVID-19 in adults and paediatric patients.<sup>10</sup>
- The [European Medicines Agency](#) has authorised Ronapreve (casirivimab+imdevimab) and Regkirona (regdanvimab). It also has Evusheld (tixagevimab/cilgavimab) under rolling review.<sup>11</sup>

### Recommendations from published guidance

- The [Australian National Taskforce](#) living guidelines recommend:
  - to consider using casirivimab plus imdevimab (Ronapreve/REGEN-COV) in seronegative patients hospitalised with moderate to critical COVID-19 (including in

- pregnant or breastfeeding women), or in mild outpatients with one or more risk factors for disease progression
- not using casirivimab plus imdevimab in seropositive patients hospitalised with moderate to critical COVID-19, in pregnant or breastfeeding women who are seropositive or in pregnant or breastfeeding women who are mild or asymptomatic outpatients
  - to consider in exceptional circumstances, casirivimab plus imdevimab in seronegative children and adolescents aged 12 years and over and weighing at least 40 kg with moderate to critical COVID-19 who are at high risk of disease progression
  - not using casirivimab plus imdevimab in seropositive children or adolescents hospitalised with moderate to critical COVID-19, or who have mild or asymptomatic COVID-19
  - to consider using sotrovimab for the treatment of COVID-19 within five days of symptom onset in adults (including pregnant and breastfeeding women) who do not require oxygen and who have one or more risk factors for disease progression
  - not routinely use sotrovimab outside of randomised trials in children and adolescents. However it can be considered for use in exceptional circumstances.<sup>12</sup>
- The [World Health Organization \(WHO\)](#) strongly recommends the use of IL-6 receptor blockers (tocilizumab or sarilumab which are monoclonal antibodies) in treating patients with severe or critical COVID-19 infection. For patients with non-severe COVID-19, they suggest treatment with casirivimab and imdevimab, conditional on the patient being at highest risk of hospitalisation. For patients with severe COVID-19, WHO suggests treatment with casirivimab and imdevimab, under the condition that the patient has seronegative status.<sup>13</sup>
  - The [National Institute of Health in the US](#) recommends using one of the following anti-SARS-CoV-2 monoclonal antibodies to treat non-hospitalised patients with mild to moderate COVID-19 who are at high risk of clinical progression: bamlanivimab plus etesevimab, casirivimab plus imdevimab; or sotrovimab.<sup>14</sup>
  - The [National Institute for Health and Care Excellence \(NICE\)](#) recommends offering a combination of casirivimab and imdevimab (Ronapreve or REGEN-COV/2) to COVID-19 patients aged 12 and over who are in hospital. Eligible patients will need to be seronegative.<sup>15</sup>
  - [The European Respiratory Society taskforce](#) suggests offering IL-6 receptor antagonist monoclonal antibody therapy to hospitalised patients with COVID-19 who require oxygen or ventilatory support (\*conditional recommendation, low quality of evidence).<sup>16</sup>
  - The [European Medicines Agency \(EMA\)](#) issued advice on the use of Lagevrio (molnupiravir), which is currently not authorised in the EU; that is can be used to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of developing severe COVID-19.<sup>17</sup>

### Evidence – systematic reviews

- Three systematic reviews on monoclonal antibodies reported:
  - A [Cochrane review](#) concluded that there was insufficient evidence regarding the effectiveness of treatment with monoclonal antibodies (bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and regdanvimab) including:
    - reduced mortality

- improved symptoms
- increased admissions to hospital
- serious or unwanted effects.<sup>18</sup>
- Bamlanivimab, casirivimab and imdevimab, sotrovimab, and CT-P59 [significantly reduced the risk of hospital admission](#) in outpatients with COVID-19 but did not have any mortality benefits.<sup>19</sup>
- [In patients with non-severe COVID-19](#), casirivimab-imdevimab probably reduces hospitalisation, and bamlanivimab-etesevimab, bamlanivimab, and sotrovimab may reduce hospitalisation.<sup>20</sup>
- 32 systematic reviews on IL-6 receptor antagonists, predominately tocilizumab, reported the following outcomes:

	Tocilizumab	Sarilumab	Siltuximab	Mepolizumab
<b>Mortality</b>	25 reviews found it may be effective at reducing mortality alone <sup>21-43</sup> and when combined with corticosteroids. <sup>44, 45</sup>  However, a living systematic review, three meta-analyses, and individually referenced observational studies did not find significant mortality benefits. <sup>32, 46-49</sup>	One review found it was associated with a reduction in mortality. <sup>23</sup>  However, one review showed no significant differences. <sup>49</sup>	Two reviews found it was associated with a reduction in mortality. <sup>23</sup>	-
<b>Mechanical ventilation</b>	12 reviews found it may be effective at reducing progression to mechanical ventilation. <sup>21, 23, 24, 26, 27, 29, 34, 36, 46-48, 50</sup>  However, four reviews found no difference at preventing mechanical ventilation. <sup>25, 28, 31, 35</sup>	One review found it was associated with a reduction in mechanical ventilation. <sup>23</sup>	One review found it was associated with a reduction in mechanical ventilation. <sup>23</sup>	
<b>ICU admission</b>	Three reviews found it may reduce risk of ICU admission. <sup>27, 34, 50</sup>  However, eight reviews found no difference in ICU admission compared with controls. <sup>25, 28, 31, 32, 35, 36, 48</sup>	One review found no effect on risk of ICU admission. <sup>23</sup>	One review found no effect on risk of ICU admission. <sup>23</sup>	
<b>Disease progression</b>	One review found it may reduce progression to severe disease. <sup>26</sup>			
<b>Clinical outcome</b>	One review found it reduces the risk of poor outcome and the risk of secondary infections. <sup>46</sup>  One review found it correlated with good prognosis in patients requiring mechanical ventilation. <sup>29</sup>		One review found clinical improvement in 33% of patients. <sup>52</sup>	One review found virology clearance and clinical outcome were significantly better. <sup>52</sup>

In brief documents are not an exhaustive list of publications but aim to provide an overview of what is already known about a specific topic. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

	Two reviews saw improvement of clinical symptoms. <sup>34, 51</sup>			
	However, three reviews found no difference in clinical recovery or length of hospital stay. <sup>33, 40</sup>			
<b>Adverse events</b>	Five reviews found it did not show a higher risk of infections or adverse events. <sup>40, 46, 48</sup>			

## Evidence – resistance to monoclonal antibody (MABs) treatment

- A [review](#) study found that monoclonal antibodies had reduced efficiency in neutralising variants of SARS-CoV-2 (Figure 1).<sup>53</sup>

Figure 1<sup>53</sup>

Table 1. The notable variants of SARS-CoV-2 and clinical differences

Pango lineages	Nextstrain clade	GISAID clade	WHO label	Potential origin (first documented sample)	Notable S mutation	Effect of variant clinically
B.1.1.7	20I (V1)	GRY	Alpha (α)	UK	69/70 del, N501Y, P681H	Higher transmissibility (~70%) and lethality (~60%). Moderate decrease of neutralization efficiency
B.1.351	20H (V2)	GH/501Y.V2	Beta (β)	South Africa	K417N, E484K, N501Y	Higher transmissibility (20–113%), significant mAb neutralization efficiency reduction
B.1.617.1	21B	G/452R.V3	Kappa (κ)	India	L452R, E484Q, P681R	Reduction in neutralization efficiency
B.1.617.2	20J (V3)	GR/501Y.V3	Delta (δ)			
B.1.1.284 (P.1)	21A	G/478K.V1	Gamma (γ)	Brazil	K417T, E484K, N501Y	Higher transmissibility (~161%) and increased lethality (~80%) and reduction in neutralization efficiency
B.1.427	21C	GH/452R.V1	Epsilon (ε)	USA	S13I, W152C, L452R	Higher transmissibility (~20%) and moderate reduction in neutralization efficiency
B.1.429						

- One preprint study reported [resistance mutations to monoclonal antibody therapy](#) with bamlanivimab.<sup>54</sup>
  - Treatment-emergent resistance mutations were more likely occur in the treatment group with 700mg bamlanivimab than the placebo group (7% versus 0%, p=0.003).
  - Individuals who had emerging monoclonal resistant virus had significantly higher pre-treatment nasopharyngeal and anterior nasal viral load.
  - There was evidence of rapid viral rebound and worsened clinical symptoms after the emergence of resistance mutations.
- A [comparative profiling study](#) involving 25 clinical-stage therapeutic antibodies found that most (14 out of 15) single antibodies were vulnerable to at least one receptor binding domain (RBD) substitution in the spike protein. Names of the individual antibodies were not disclosed due to confidentiality agreement with the developers who donated the antibodies under investigation.<sup>55</sup>
  - Despite vulnerability to substitution, most combination and polyclonal therapeutic antibodies remained potent.
  - Resistance against an emerging variant is found to be more likely if there is a key substitution in the spike protein of SARS-CoV-2 variants. However, the degree of the resistance can be modified by the other substitutions that may reside outside of the RBD.

- One study reported that the [Gemma \(P.1\) variant](#) virus (both pseudovirus and authentic) can be markedly or completely resistant to multiple neutralizing monoclonal antibodies, including casirivimab, bamlanivimab and etesevimab. Imdevimab was the only antibody that retained neutralizing activity.<sup>56</sup>
- One preprint study reported increased resistance of [Alpha \(B.1.1.7\) and Beta \(B.1.351\)](#) to monoclonal antibody neutralization.<sup>56, 57</sup>
  - Alpha (B.1.1.7) is refractory to neutralisation by most monoclonal antibodies engaging the N-terminal domain (NTD) of spike and relatively resistant to several monoclonal antibodies engaging the RBD.
  - Beta (B.1.351) is refractory to neutralisation by most monoclonal antibodies to the N-terminal domain (NTD) of spike and multiple monoclonal antibodies to the RBD.
    - The neutralisation activities of bamlanivimab and casirivimab were completely or markedly abolished against mutations in the Beta (B.1.351) variant. Imdevimab, along with other monoclonal antibodies that directed to lower aspects of the 'inner side' or to the 'outer side', retained their neutralising activities.
- One study found that several [monoclonal antibodies](#) engaging the RBD or N-terminal domain (NTD) failed to neutralise Beta (B.1.351) or recombinant variants with an E484K spike mutation.<sup>58</sup>
- One study from Japan reported that most [monoclonal antibodies](#) retained their neutralising activities against Alpha (B.1.1.7) variant. However, they had significantly reduced neutralising efficacy against Beta (B.1.351) and Gemma (P.1) variants. Monoclonal antibodies with a high affinity for the RBD retained their effectiveness in neutralising both the Beta (B.1.351) and Gemma (P.1) variants.<sup>59</sup>
- Another study found that many monoclonal antibodies had [reduced neutralising potency](#) against Alpha (B.1.1.7) variant. Cocktails of the monoclonal antibodies overcame the resistance from the variant to a single antibody.<sup>60</sup>
- One study found that the [Delta \(B.1.617\) variant](#) is resistant to bamlanivimab.<sup>61</sup>
- In a [multicentre, retrospective cohort study](#) from Saudi Arabia involving 738 critically ill patients with COVID-19, patients who received tocilizumab (n=262) had similar rates of microbial isolation, the emergence of resistant organisms, or the detection of carbapenem-resistant enterobacteriaceae (CRE) organisms to those in the control group (n=476).<sup>62</sup>
- One study identified a monoclonal antibody, [S2H97](#), that can retain neutralising activities against known variants of SARS-CoV-2.<sup>63</sup> Another antibody, S2E12, was also found to have modest breadth in cross-neutralising known variants. Another study from [Australia](#) identified monoclonal antibodies that are unaffected by the variants of SARS-CoV-2 in their neutralising activities.<sup>64</sup>

To inform this brief, PubMed and Google searches were conducted using terms related to COVID-19 and monoclonal antibodies on 25 November 2021.

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