



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

9 December 2022  
EMA/931457/2022  
Emergency Task Force

## ETF statement on the loss of activity of anti-spike protein monoclonal antibodies due to emerging SARS-CoV-2 variants of concern

Since the declaration of the COVID-19 public health emergency in early 2020, four monoclonal antibody products have been approved in the European Union for the prevention and treatment of COVID-19<sup>1,2,3,4</sup>. A recommendation under Article 5(3) was issued for a fifth product<sup>5</sup>.

These monoclonal antibody therapies are composed of one or more different neutralising antibodies. They are designed to bind to the spike protein of SARS-CoV-2 and thereby interfere with the ability of the virus to attach to and enter the host cells. They have been proven to prevent the risk of symptomatic COVID-19 infection in the context of pre-exposure or post-exposure prophylaxis<sup>1,2</sup>, and to reduce the risk of progression to severe disease, hospitalisation and death in patients with early disease not requiring supplemental oxygen and who are at an increased risk for progressing to severe COVID-19 disease<sup>1,2,3,4</sup>.

The SARS-CoV-2 virus has continuously evolved and several variants of concern have emerged since the initial outbreak due to the original SARS-CoV-2 virus WUHAN strain (Wuhan-Hu-1). These variants carry mutations in the spike protein that reduce the ability of the monoclonal antibodies to bind, which may reduce their efficacy. With the first variants of concern that were identified (Alpha, Beta, Gamma and Delta), some but not all of the monoclonal antibodies showed reduced virus neutralisation activity<sup>6,7</sup>. The newer SARS-CoV-2 variants (i.e. Omicron and several Omicron subvariants [BA.1, BA.2, BA.4 and BA.5]) are even less susceptible to the monoclonal antibodies based on reductions in neutralisation activity *in vitro*<sup>6,7,8,9</sup>. However, it is not known to what extent this decreased *in vitro* neutralisation activity against variants of concern affects clinical efficacy, as the relationship between viral susceptibility *in vitro* and serum concentration of the monoclonal antibodies *in vivo* is not completely understood, and there are no clinical trial data available to determine whether clinical efficacy is reduced. Moreover, at present it is unknown if the efficacy of the monoclonal antibodies against variants of concern can be restored by administering higher doses than those currently recommended.

Recent virus neutralisation data show very marked reductions in susceptibility against Omicron sublineages BA.4.6, BA.2.75.2, XBB, BQ.1 and BQ.1.1 indicating an escape to all of the EU-approved monoclonal antibodies<sup>9,10,11,12</sup>. Based on modelling data published by ECDC on 20<sup>th</sup> October 2022 the BQ.1/BQ.1.1 variant will become dominant in the EU by the end of 2022<sup>13</sup>.

Consequently, the use of monoclonal antibodies for the prevention or treatment of COVID-19 in patients at increased risk for progressing to severe COVID-19 will likely not provide a clinical benefit in



regions of the EU in which BQ.1.1, BQ.1, BA.4.6, BA.2.75.2, XBB and BJ.1 are spreading. Furthermore, it remains unknown to what extent the approved monoclonal antibodies that have decreased neutralisation activity against the Omicron sublineages BA.1, BA.2, BA.4 and BA.5 will be clinically effective.

In view of this, healthcare professionals are advised to check the current epidemiological situation in their region<sup>14</sup> and to consider alternative antiviral treatment options like Nirmatrelvir/Ritonavir (Paxlovid)<sup>15</sup> and Remdesivir (Veklury)<sup>16</sup> that are approved in the EU for the treatment of COVID-19 in patients who are at increased risk for progressing to severe COVID-19 and do not require supplemental oxygen. These therapies are expected to retain their antiviral activity against the emerging variants of concern, as their activity has not been affected so far by the mutational pattern of currently circulating variants of concern<sup>12,17,18,19</sup>.

Ensuring availability and rapid access to Nirmatrelvir/Ritonavir and Remdesivir is of paramount importance to protect vulnerable patients who are at an increased risk of developing severe forms of the disease and require hospitalisation. Due to the current epidemiological situation, member states are encouraged to ensure rapid access to these antiviral treatment options.

ETF will continue to monitor the epidemiological situation in the EU and may adapt the product information of monoclonal antibodies in due course.

## References:

- 1: Evusheld EPAR: [Evusheld | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/documents/overview/evusheld-epar-medicine-overview_en.pdf), [https://www.ema.europa.eu/documents/overview/evusheld-epar-medicine-overview\\_en.pdf](https://www.ema.europa.eu/documents/overview/evusheld-epar-medicine-overview_en.pdf)
- 2: Ronapreve EPAR: [Ronapreve | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/documents/overview/ronapreve-epar-medicine-overview_en.pdf), [https://www.ema.europa.eu/documents/overview/ronapreve-epar-medicine-overview\\_en.pdf](https://www.ema.europa.eu/documents/overview/ronapreve-epar-medicine-overview_en.pdf)
- 3: Xevudy EPAR: [Xevudy | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/documents/overview/xevudy-epar-medicine-overview_en.pdf), [https://www.ema.europa.eu/documents/overview/xevudy-epar-medicine-overview\\_en.pdf](https://www.ema.europa.eu/documents/overview/xevudy-epar-medicine-overview_en.pdf)
- 4: Regkirona EPAR: [Regkirona | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/documents/overview/regkirona-epar-medicine-overview_en.pdf), [https://www.ema.europa.eu/documents/overview/regkirona-epar-medicine-overview\\_en.pdf](https://www.ema.europa.eu/documents/overview/regkirona-epar-medicine-overview_en.pdf)
- 5: Article 5(3) opinion bamlanivimab and etesevimab for the treatment of COVID-19, <https://www.ema.europa.eu/en/news/ema-issues-advice-use-antibody-combination-bamlanivimab-etesevimab>
- 6: Cox et al., October 2022, Nature reviews microbiology: *SARS-CoV-2 variant evasion of monoclonal antibodies based on in vitro studies*, DOI: <https://doi.org/10.1038/s41579-022-00809-7>
- 7: van der Straten et al., March 2022, Front. Med. Technol.: *Optimising of anti-SARS-CoV-2 neutralising antibody therapies: roadmap to improve clinical effectiveness and implementation*. DOI: <https://doi.org/10.3389/fmedt.2022.867982>
- 8: Cao et al., June 2022, Nature: *BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection*, DOI: <https://doi.org/10.1038/s41586-022-04980-y>
- 9: Cao et al., October 2022, bioRxiv preprint: *Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution*, DOI: <https://doi.org/10.1101/2022.09.15.507787>
- 10: Sheward et al., October 2022, The Lancet: *Omicron sublineage BA.2.75.2 exhibits extensive escape from neutralising antibodies*, DOI: <https://doi.org/10.1016/>
- 11: Arora et al., Nov. 2022, The Lancet Infectious diseases: *Omicron sublineage BQ.1.1 resistance to monoclonal antibodies*, DOI: [https://doi.org/10.1016/S1473-3099\(22\)00733-2](https://doi.org/10.1016/S1473-3099(22)00733-2)
- 12: Imai et al., December 2022, *Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB*, DOI: <https://doi.org/10.1056/nejmc2214302>
- 13: ECDC homepage: [Spread of the SARS-CoV-2 Omicron variant sub lineage BQ.1 in the EU/EEA \(europa.eu\)](https://www.ecdc.europa.eu/en/covid-19/country-overviews)
- 14: Weekly country updates, ECDC homepage <https://www.ecdc.europa.eu/en/covid-19/country-overviews>
- 15: Paxlovid EPAR: [Paxlovid | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/documents/overview/paxlovid-epar-medicine-overview_en.pdf)
- 16: Veklury EPAR: [Veklury | European Medicines Agency \(europa.eu\)](https://www.ema.europa.eu/documents/overview/veklury-epar-medicine-overview_en.pdf)
- 17: Takashita et al., Nov. 2022, NEJM: *In vitro efficacy of antiviral agents against omicron subvariant BA.4.6*, DOI: <https://doi.org/10.1056/nejmc2211845>

18: Takashita et al., March. 2022, NEJM: Efficacy of antibodies and antiviral drugs against COVID-19 Omicron variant, DOI: <https://doi.org/10.1056/nejmc2119407>

19: Vangeel et al., Feb. 2022, Antiviral research: Remdesivir, Molnupitavir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern, DOI: <https://doi.org/10.1016/j.antiviral.2022.105252>