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Emergency Task Force

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

An update

Since the declaration of the COVID-19 public health emergency in early 2020, four monoclonal antibody products have been approved in the European Union (EU) for the prevention and treatment of COVID-19[1-4,6]. A recommendation under Article 5(3) was issued for a fifth product[5]. Most recently, a sixth product, Kavigale (sipavibart), has received a positive opinion, marking the first positive opinion for a monoclonal antibody after the emergence of the SARS-CoV-2 Omicron variants[6].

These monoclonal antibody therapies are composed of one or more different antibodies. They are designed to bind to the SARS-CoV-2 spike protein and thereby interfere with the ability of the virus to attach to and enter the host cells. These products have been approved to prevent the risk of symptomatic COVID-19 infection in the context of pre-exposure or post-exposure prophylaxis[1,2,6], and/or 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 of progressing to severe COVID-19 disease[1-4].

The SARS-CoV-2 virus is continuously evolving. Several new variants of concern have emerged since the initial outbreak due to the original SARS-CoV-2 virus WUHAN strain (Wuhan-Hu-1). Many of these variants carry mutations in the spike protein that reduce the ability of the monoclonal antibodies to bind and thereby reducing their efficacy. This evolution of the SARS-CoV-2 virus resulted in marked reductions in susceptibility of the Omicron sublineages (e.g. BA.4.6, BA.2.75.2, XBB, BQ.1 and BQ.1.1), abolishing the clinical efficacy of all EU-approved monoclonal antibodies at that time[7-14]. Due to these findings, ETF issued a statement in December 2022, warning that the four approved and one recommended monoclonal antibodies may not provide clinical benefit in regions of the EU where these emerging strains were spreading[15].

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Since the release of this statement various new SARS-CoV-2 variants have evolved, including different XBB variants (XBB.1.5[16], XBB.1.16[16], XBB.2.3[16], BA.2.86[17]), JN.1[18], KP.1[19], KP.2[19,20], KP.3[19,21], LB1[21], KP.3.1.1[22], and XEC[23]. Importantly, none of the four initially approved or recommended monoclonal antibodies have regained neutralisation capacity against these new variants [24-26]. Therefore, the use of these monoclonal antibodies should be avoided as it is unlikely that they will provide any clinical benefit.

Recently, Kavigale (sipavibart), another anti-spike protein monoclonal antibody, received a positive opinion by CHMP in the EU[6]. Sipavibart is based on the same platform technology as one of the previously approved monoclonal antibody products but has demonstrated a broader neutralising activity across all historical and many contemporary SARS-CoV-2 variants, including XBB.1.5, XBB.1.16, XBB.2.3 and BA.2.86. However, based on *in vitro* data sipavibart has no antiviral activity against SARS-CoV-2 variants carrying the F456L mutation.

The positive opinion of Kavigale was based on the single pivotal, randomised, double-blinded SUPERNOVA main cohort efficacy study in adolescents ≥12 years of age or adults with clinically significant immunosuppression. In this study, sipavibart treatment resulted in an overall 30% relative risk reduction. During the study, viruses carrying the F456L mutation emerged, which are not neutralised by sipavibart. While no protective efficacy is anticipated against viruses carrying the F456L mutation, sipavibart showed a 35% relative risk reduction against variants not carrying the F456L mutation[6].

Data published by the European Centre for Disease Prevention and Control (ECDC) in November 2024 indicate that KP.3 is currently the major SARS-CoV-2 variant circulating in the EU/EEAA with other variants such as BA.2.86, KP.2, KP.1 and KP 3.1.1 co-circulating at low percentages [27]. All these variants, except for BA.2.86, carry the F456L[28] mutation against which sipavibart has shown no antiviral activity *in vitro* and is not anticipated to provide protection.

Consequently, the use of sipavibart for the prevention of COVID-19 in patients who are immunocompromised and for whom COVID-19 vaccination is not recommended will likely not provide any clinical benefit in regions of the EU where variants carrying the F456L mutation are spreading. The review process was completed acknowledging that the anticipated clinical benefit of this monoclonal antibody is continuously changing as the virus evolves. For this reason, a statement was included in the summary of product characteristics (SmPC) clearly stating the anticipated lack of efficacy against SARS-CoV-2 variants harbouring the F456L mutations[6]. This is to ensure that clinicians are aware and do not use sipavibart when variants carrying the F456L are circulating or dominant. ETF reiterates that sipavibart should not be used if F456L variants are predominantly in circulation.

In view of this, healthcare professionals are advised to check the current epidemiological situation in their region[29]. If variants carrying the F456L mutation are prevalent, vaccination remains the best option to prevent disease, also in immunocompromised patients in whom the immune response may be reduced. In case of infection, antiviral treatment options are available, such as nirmatrelvir/ritonavir (Paxlovid)[30] and remdesivir (Veklury)[31] that are approved in the EU for the treatment of COVID-19 in patients who are at increased risk of progressing to severe COVID-19. These therapies are expected to retain their antiviral activity against the currently circulating variants, as so far their activity has not been impacted by the mutational pattern of currently circulating variants of concern[16,32-35].

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

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