Department of Health & Social Care

From the Rt Hon Steve Barclay MP
Secretary of State for Health and Social Care

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Gemma Peters
Chief Executive
Blood Cancer UK

05 September 2022

Dear Gemma et al,

Thank you for your letters of 28 July and 23 August on Evusheld.

I understand your concerns and would like to assure you that Government efforts remain absolutely focused on protecting the most vulnerable, including through prioritised access to vaccines, treatments, and testing.

The expert panel who advises Government has made clear that there is insufficient evidence available at this time to support procurement and deployment of Evusheld through emergency procedures. When MHRA gave conditional Marketing Authorisation to Evusheld on 17th March, following trials conducted during the Delta wave, it noted a lack of data regarding dose and efficacy against Omicron. A number of other countries' regulatory authorities, including the EMA and the FDA, have noted similar issues, although many of those countries who had already procured Evusheld have decided to continue using it, in most cases doubling the dose to 600mg.

There have been similar concerns about the effectiveness of other monoclonal antibodies to emerging COVID-19 variants, on the basis of in vitro (laboratory) testing, leading to appropriate re-evaluation prior to recommendation for widespread deployment or continuation of use. In some instances, the in vitro data have been so unequivocal in demonstrating lack of effectiveness that a product has been promptly withdrawn; in the case of Evusheld, a number of different groups have conducted laboratory tests with different Omicron sub-variants and there is ongoing uncertainty about how these results might translate to clinical effectiveness.

To address your specific questions, the decision has been made not to procure Evusheld at this time drawing on expert advice from RAPID C-19 and a UK National Expert Policy Working Group as well as DHSC officials, all of whom have collectively concluded that there is insufficient evidence of benefit to recommend deployment at this time. In their expert advice, RAPID C-19 note that 'the risks of proceeding to patient access are considered to outweigh the risks of not providing this treatment in the current pandemic context'. More detail on RAPID C-19 can be found in Annex A.

RAPID C-19 have considered the evidence base for Evusheld 11 times in 18 months, starting in February 2021, and are keeping it under active review, including through monitoring the emerging data. They have considered a full range of evidence, including clinical trial data, in vitro analysis and all the observational studies in the appendix to your letter of 23rd August.

As the authors note themselves, there are limitations to these studies. For example, "results may not be generalizable to a larger population of patients" (Young-Xu et al); "the study did not take into account differences between the 2 groups regarding other antiviral treatments available, such as nirmatrelvir, that may also affect severe disease prevalence" (Kertes et al); and "The limitations of our study include its observational nature, retrospective design, lack of ability to detect asymptomatic breakthrough infections and possible differences between the tixagevimab/cilgavimab and control groups that could have influenced the rate of breakthrough infection." (Jurdi et al). In addition to the inherent limitations of observational data, particularly on small sample sizes, it should also be noted that most of these studies are pre-prints (therefore have not been scrutinised through peer review). There are also concerns with the methodology of a number of studies, as it is not clear that the comparator group is adequately matched (such that the Evusheld group may be at inherently lower risk of adverse outcomes), or where the follow-up period is substantially shorter for the Evusheld group compared to the control group (such that the Evusheld group would have had a shorter time to experience a COVID-19 infection). So, whilst some of the findings may appear encouraging, the view from our experts remains that the methodological and reporting limitations of these papers means there is insufficient evidence from the clinical data to recommend deployment at this time.

The Chief Medical Officer is content that the correct process for providing clinical advice has been followed and agrees that Evusheld should now be appraised by the National Institute for Health and Care Excellence (NICE) following the usual process for drugs being made available to NHS patients.

In terms of the patients who stand to benefit from a safe and effective prophylactic, your letter refers to 500,000 immunosuppressed people in the UK. Notwithstanding the questions on efficacy and duration of effect, it is highly unlikely that supply could be made available to the UK for all these patients in Autumn/Winter 2022, particularly as doubling the dose to 600mg is recommended for use against Omicron.

Moreover, it is also unlikely to be suitable or needed for this size of cohort. Evidence shows that different patient groups with immunosuppression have different levels of vaccine response. Identifying the correct cohorts (for example those with unpredictable, low or no antibody response) would be essential, even if questions on effectiveness were sufficiently answered. Evusheld is not necessary for those patients who have a protective antibody response to COVID-19 vaccination. In order to understand better who within this group mounts a vaccine response, we are exploring the possibility of piloting a programme to test antibody levels in immunosuppressed patients. This could help develop a more accurate understanding of potential cohorts for prophylactic treatments in future and could also help provide reassurance to some patients by identifying any who have mounted a protective antibody response following vaccination. Officials will follow up with patient groups separately to seek input into the development of this potential programme.

In order to gain further evidence, our clinical advisers have also recommended a trial is considered as a route to answering outstanding questions on the link between in vitro tests and clinical outcomes for current and future variants, which is currently not known, together with evaluating the effectiveness and safety of a dose of 600mg, as this was not tested in the randomised controlled trials.

I personally met senior AstraZeneca leaders on Thursday 18 August and the DHSC Chief Scientific Adviser has had frequent discussions with science leaders in AstraZeneca, including a meeting on Friday 26 August to discuss data from existing observational studies in detail. We remain committed to close working with the company, and I greatly value the continued partnership we share with AstraZeneca and recognise the very positive impact they have made throughout the pandemic and beyond.

Yours ever,

RT HON STEVE BARCLAY MP

Annex A

RAPID C-19

RAPID C-19 (Research to access pathway for investigational drugs for COVID-19) is a multi-agency initiative set up in response to the pandemic which aims to get treatments for COVID-19 to NHS patients quickly and safely. Its membership includes the UK's main healthcare agencies including the Medicines and Health products Regulatory Agency (MHRA), NICE, NHS England and NHS, the National Institute for Health Research (NIHR) and the Devolved Governments. The NHS had overall responsibility for establishing RAPID C-19, and NICE chair the Senior RAPID C-19 Group and provide secretariat support.

As of June, RAPID C-19 had around 90 topics in active monitoring and the Oversight Group have considered the evidence in detail for those drugs that have evidence of benefit, since it was stood up in April 2020. Of these, nine have led to a positive recommendation to the four UK Chief Medical Officers that direct deployment outside of the more normal processes should be considered.

Further information on RAPID C-19 can be found here: Research to access pathway for investigational drugs for COVID-19 (RAPID C-19) | NICE

Reporting:

RAPID C-19 is a multi-agency initiative including NIHR, NICE, MHRA, NHSE-I and representatives from the Devolved Governments. The agencies aim to ensure safe and timely patient access to treatments that show evidence of benefit in preventing and treating COVID-19.

Where good evidence of efficacy of a treatment is sufficient for further action to be taken, the Oversight Group's assessment of the evidence and suggested next steps are summarised in a briefing to the Chief Medical Officer.

Expert Working Group

In parallel to the formation of RAPID C-19, NHSE extended its existing national clinical policy making process to cover COVID-19 therapeutics. As part of this process a National Expert Working Group (EWG) was created to support development of a national clinical policy, with a focus on clinical effectiveness and eligibility criteria. An EWG is convened to develop a national clinical policy for a specific drug, or sometimes to provide further relevant advice. The EWG is chaired by a senior NHS staff member, and the membership includes UK-wide national experts and frontline clinicians, officials from the Devolved Governments are involved throughout. EWGs have focused on therapeutic agents but, more recently, have also considered prophylactic agents.

Annex B: NICE appraisal process

- NICE provides evidence-based, rigorous evaluation of the clinical and cost effectiveness of medicines for use in the NHS.
- NICE began consulting stakeholders on the draft scope for an evaluation of the clinical and cost effectiveness of Evusheld for preventing COVID-19 in July 2022, and it was formally referred to NICE by the Department on 10 August 2022. The NICE appraisal has begun this month, with draft guidance expected in April 2023.
- NICE, in discussion with AstraZeneca, has taken steps to expedite the appraisal process by bringing forward the deadline for the company's evidence submission so that it is able to issue guidance to the NHS as quickly as possible.
- Further information on the NICE technology appraisal process can be found here. More detailed information on the Evusheld appraisal process will be provided on NICE's website shortly.