Use of tixagevimab/cilgavimab (Evusheld) for pre-exposure prophylaxis against COVID-19: Briefing for Chief Medical Officer (CMO)

Date: 25 May 2022

Background

Tixagevimab/cilgavimab (Evusheld) was granted Conditional Marketing Authorisation for pre-exposure prophylaxis (PrEP) against COVID-19 by the Medicines and Healthcare Regulatory Agency (MHRA) on 17 March 2022. Consequently, on 26 April 2022, a national expert group was convened to discuss whether a UK clinical commissioning policy should be considered. The expert group recommended that tixagevimab/cilgavimab should not progress to clinical deployment due to significant scientific uncertainty over effectiveness in the current pandemic context, and that further research evidence was needed. An advisory briefing was consequently provided to the CMO, dated 26 April 2022.

Since then, new data have emerged and the expert group was asked to reconvene and reassess its advice. The meeting of this group was held on 19 May 2022. A list of attendees is provided in Appendix 1 and included four nation representation.

Position of other organisations and nations

1) **World Health Organization (WHO)**: There is no reference to tixagevimab/cilgavimab for PrEP against COVID-19 in the WHO Therapeutics and COVID-19: living guideline (last updated on 22 April 2022).
2) **National Institute for Health and Care Excellence (NICE):** There is no current reference to tixagevimab/cilgavimab for PrEP against COVID-19 in NICE's COVID-19 rapid guideline: Managing COVID-19 (last updated on 19 May 2022).
3) **National Institutes of Health (NIH, USA):** The NIH COVID-19 Treatment Guidelines Panel recommends tixagevimab/cilgavimab as SARS-CoV-2 PrEP for adults and adolescents who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection and are at particular risk. The original dosage regimen was 150mg tixagevimab and 150mg cilgavimab delivered in two consecutive intramuscular injections. Subsequently, based on modelled assessment of the in-vitro neutralising activity of tixagevimab/cilgavimab against the Omicron BA.1 and BA.1.1 subvariants, the **US Food and Drug Administration (FDA)** revised the authorised dosage regimen to an initial dose of 300mg of tixagevimab and 300mg of cilgavimab. The FDA Emergency Use Authorization states that individuals who have received tixagevimab 150mg plus cilgavimab 150mg should be given a second dose as soon as possible (guidance last updated on 29 April 2022). The NIH recommends this increased dosage for PrEP against COVID-19.
4) **Government of Canada**: Health Canada authorised tixagevimab/cilgavimab on 14 April 2022 for PrEP against COVID-19 in adults and adolescents who are immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination, or for whom COVID-19 vaccination is not recommended.
5) **Australian Government's Department of Health**: The Therapeutic Goods Administration (TGA) on 24 February 2022 granted provisional approval of tixagevimab/cilgavimab for PrEP against COVID-19 in people aged 12 years and older and at particular risk.

It is important to note that the above licensing/authorisation decisions or professional guidance do not necessarily reflect deployment of tixagevimab/cilgavimab.

Discussion

In advance of the expert group meeting, new documents and data for the use of tixagevimab/cilgavimab as PrEP against COVID-19 were circulated to all invitees. This information included new pharmacokinetic (PK) data from UKHSA and Oxford University on the activity of tixagevimab/cilgavimab against BA.2, and a preprint from China studying BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. In advance of the meeting, the chair spoke with [s40(2)] who could not participate in the meeting due to a newly declared direct conflict of interest.

The group discussed in detail the following areas:

1) **Summary of current clinical evidence**
   <[s40(2)]> Chair of the Prophylaxis Oversight Group (DHSC), presented a summary of recent evidence and outlined his view on progression to routine deployment of tixagevimab/cilgavimab as PrEP against COVID-19. Discussion generated the following key points:
   - There is reasonable clinical data that tixagevimab/cilgavimab is effective as PrEP against pre-Omicron variants.
   - Only pre-clinical data and antiviral models are available for BA.x variants.
   - There are concerns regarding reduction in efficacy in the neutralising activity of tixagevimab/cilgavimab for newer (sub)variants.
   - There are concerns that high-risk groups may modify their behaviour to less risk-avoidant after taking a prophylactic agent – with particular implications if such an agent is of limited effectiveness.
   - There is insufficient evidence of clinical effectiveness against Omicron variants to justify widespread deployment in the present UK context.

2) **Assessment of tixagevimab/cilgavimab neutralisation of live SARS-CoV-2 activity**
   <[s40(2)]> and <[s40(2)]> from the UK Health Security Agency (UKHSA) presented evidence from Virus Neutralization Assays (VNA). Their findings were discussed:
   - The differential in neutralisation concentrations in the studies performed on tixagevimab/cilgavimab against the BA.x variants is small compared to neutralisation concentrations reported for the other variants tested. This suggests that tixagevimab/cilgavimab may have equivalent clinical effect against the panel of variants tested, including BA.x strains.
   - There is insufficient information (e.g. limited samples) from current UKHSA testing to draw definitive conclusions for a clinical policy.

3) **Interpretation of pharmacodynamic and pharmacokinetic (PD/PK) data**
   <[s40(2)]> presented an updated pharmacokinetic overview of tixagevimab/cilgavimab in the context of in-vitro neutralising activity against BA.x variants, including consideration of all new PD/PK data since the previous meeting:
   - The expert group was reminded that tixagevimab/cilgavimab antibodies have additional modifications to obviate the effector functions. Therefore, direct neutralisation is the only mechanism of action.
   - In-vitro data has demonstrated significantly compromised activity for tixagevimab/cilgavimab against the BA.2 subvariant of Omicron.
   - There are major uncertainties related to the required tissue concentration to achieve neutralisation of SARS-CoV-2, especially in the lungs. There is a need for clinical data to define serum targets for efficacy.

- Both antibodies in tixagevimab/cilgavimab were substantially compromised with respect to BA.1 Omicron to an extent that there could be no reasonable expectation of parity with pre-omicron variants. For cilgavimab the neutralisation activity against BA.2 Omicron was restored such that it maintains neutralisation activity comparable to that against the pre-Omicron variants for which it was clinically studied. However, for tixagevimab neutralisation of BA.2 Omicron remains compromised. Therefore, the combination effectively acts as prophylaxis monotherapy against COVID-19, for which clinical trial data does not exist.

Recommendation

There was an extensive discussion following the presentations which concluded that in the absence of good clinical effectiveness data, the in-vitro data are insufficient to determine a routine deployment decision. There is, at present, significant scientific uncertainty and clinical equipoise around the efficacy of tixagevimab/cilgavimab as PrEP against COVID-19, especially in the current pandemic context in the UK.

The chair asked members of the group (but not observers) to vote on whether routine deployment could be recommended.

1) There was unanimous agreement from the national expert group that tixagevimab/cilgavimab should not currently progress to routine deployment as PrEP against COVID-19.
2) The necessity of generating meaningful clinical data was reiterated. There is the need for more in-human data on the clinical effectiveness of tixagevimab/cilgavimab in the current UK population and present pandemic context. This could be in the form of a pragmatic clinical trial, which would likely be observational using a high-risk patient population. Within such a trial there is an imperative to examine PD/PK data in a sub-group of high-risk patients, so as to helpfully inform clinical pharmacological knowledge.

Appendix 1

COVID-19 tixagevimab/cilgavimab (Evusheld) pre-exposure prophylaxis National Expert Group Meeting 19/05/2022

Attendees

Professor Anthony Kessel (Chair) (AK)	Clinical Director, National Clinical Policy, NHS England and NHS Improvement
<[s40(2)]>	<[s40(2)]> Liverpool School of Tropical Medicine
<[s40(2)]>	<[s40(2)]> UK Health Security Agency (UKHSA)
<[s40(2)]>	<[s40(2)]> UKHSA
<[s40(2)]>	<[s40(2)]> University of Liverpool
<[s40(2)]>	<[s40(2)]> Alder Hey Children's Hospital
<[s40(2)]>	<[s40(2)]> Royal Free Hospital
<[s40(2)]>	<[s40(2)]>
<[s40(2)]>	<[s40(2)]> NHS England and NHS Improvement. <[s40(2)]> The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Dr Simon Barton (SB)	NHS England Medical Director for London, <[s40(2)]> Chelsea and Westminster Hospital
<[s40(2)]>	<[s40(2)]> Llywodraeth Cymru/ Welsh Government
<[s40(2)]>	<[s40(2)]> University of Glasgow
<[s40(2)]>	<[s40(2)]> COVID-19 Therapeutics, UKHSA
<[s40(2)]>	Department of Health, Northern Ireland
<[s40(2)]>	<[s40(2)]>, Welsh Government
<[s40(2)]>	<[s40(2)]> The Scottish Government
<[s40(2)]>	<[s40(2)]> Llywodraeth Cymru/Welsh Government
<[s40(2)]>	Member of the COVID-19 Prophylaxis Oversight Group
<[s40(2)]>	<[s40(2)]>, Specialised Commissioning, NHS England and NHS Improvement
<[s40(2)]>	<[s40(2)]> NHS England and NHS Improvement
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<[s40(2)]>	<[s40(2)]> Specialised Commissioning, NHS England and NHS Improvement
<[s40(2)]>	<[s40(2)]> Specialised Commissioning, NHS England and NHS Improvement

Observers

<[s40(2)]>	<[s40(2)]> COVID-19 Centre for Guidelines, NICE

<[s40(2)]>	Department of Health and Social Care Observer
<[s40(2)]>	Department of Health and Social Care Observer