Use of tixagevimab/cilgavimab (Evusheld) for pre-exposure prophylaxis against COVID-19: Briefing for Chief Medical Officer (CMO) [Date: 26 April 2022]

Background

Following the recent Conditional Marketing Authorisation issued by the Medicines and Healthcare products Regulatory Agency (MHRA) for the use of tixagevimab/cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP) against COVID-19, a national expert group was convened to discuss whether a UK Clinical Commissioning Policy should be considered at this point. The meeting of this group was held on 26 April 2022. A list of attendees is provided and included representatives across all four nations [Appendix].

Discussion

The group discussed the following areas, with summaries provided below. A statement was read out by the Chair from <[s40(2)]>, Chair of the COVID-19 Prophylaxis Oversight Group, who was unable to attend in person.

1) **Evidence underpinning the marketing authorisation decision**
Results from the PROVENT study (n=5197), which investigated a single dose of tixagevimab/cilgavimab (Evusheld) in adults at increased risk of an inadequate response to vaccination against COVID-19, an increased risk of exposure to SARS-CoV-2, or both, indicated that PrEP with tixagevimab/cilgavimab resulted in a relative risk reduction of 76.7% ($p<0.001$) against development of symptomatic COVID-19 compared with placebo. Post-hoc analysis at a median follow-up period of 6 months showed COVID-19 hospitalisation rated of 0% and 0.4% in the treatment and placebo arms respectively, regardless of prior vaccination or unblinding. The group noted that this evidence was from patients infected with pre-Omicron SARS-CoV-2 variants, and the relevance of this data in the context of the current Omicron variant was debated. The low event rate (in both placebo and treatment arms), was also noted.

2) **Activity against the Omicron variant of SARS-CoV-2**
The in-vitro pharmacokinetic and pharmacodynamic (PK/PD) analyses of various neutralising monoclonal antibodies (nMABs) against SARS-CoV-2 variants were discussed reporting that while the neutralisation activity of cilgavimab against the Omicron BA.2 subvariant was preserved, the neutralisation activity of tixagevimab against the same subvariant was significantly reduced. There was a >100-fold reduction in the neutralisation activity of both antibodies against the BA.1 subvariant. Administration of tixagevimab and cilgavimab at twice the licensed dose may produce neutralisation activity against BA.2 at similar levels to the published literature. However, this would be in the context of monotherapy with cilgavimab, with possible implications for downstream development of new/escape mutants.

3) **Cohorts to be considered for PrEP and potential role of serum antibody status**
Representatives from the Department of Health and Social Care (DHSC)-commissioned Independent Advisory Group (IAG) on highest risk patient cohorts discussed the cohort groups that might, in principle, be considered for PrEP. The IAG's recommendations, including around serology testing, are summarised below. It should be noted that the IAG did not assess the evidence of effectiveness, just the potential cohorts for consideration.

Cohort group	Description	Considerations for serology testing
A1	Known failure of vaccination	Should receive PrEP irrespective of serology status, therefore testing is of less importance
A2	Anticipated failure of vaccination	
B	Anticipated sub-optimal vaccination response	Vaccination response may be linked to serology status, therefore antibody testing may play a more important role.

The national expert group noted that there was poor representation of patients within the cohorts above in the study population of the PROVENT trial.

4) Cost-effectiveness analysis

Early health economic analyses, including around numbers needed to treat (to prevent hospitalisation) were presented by DHSC. Current hospitalisation rates due to COVID-19 are estimated to be at 2-3% and the group noted that the hospitalisation rates reported in the PROVENT study were considerably lower than this.

Conclusions

1) Not for immediate progression to deployment

The decision from the group was that there was insufficient evidence at present to support progression to the development of a UK-wide Clinical Commissioning Policy for the deployment of tixagevimab/cilgavimab for PrEP in the context of the current dominant BA.2 subvariant. This was a majority rather than unanimous decision, with one member of the group in support of progression to deployment.

2) Further evidence generation

The group noted the unmet need of the immunocompromised patients outlined by the IAG and proposed the expeditious establishment of a platform trial to support evidence generation in this group of patients at highest risk within the current UK pandemic context. The group recommended that the study design be future-proofed to enable the addition of other PrEP (or therapeutic) agents to the study and be applicable to other new (sub)variants as they emerge.

3) Option for highest risk group deployment

An option that the CMO might consider is offering access to the treatment through deployment for the small number of patients in category A1 while further evidence is gathered in the larger A2 and B groups. This group are those patients in the highest risk therapeutic cohort who have been unable to complete a vaccination schedule.

Appendix

COVID-19 tixagevimab/cilgavimab (Evusheld) pre-exposure prophylaxis National Expert Group Meeting 26/04/2022

Attendees

1) Professor Anthony Kessel – NHS England and Improvement, Clinical Director National Clinical Policy, Specialised Commissioning (Chair)
2) <[s40(2)]> – <[s40(2)]> Alder Hey Children's Hospital
3) <[s40(2)]> – <[s40(2)]> The Newcastle Upon Tyne Hospitals NSH Foundation Trust
4) <[s40(2)]> – <[s40(2)]>, Royal Free Hospital
5) <[s40(2)]> – <[s40(2)]>, University of Oxford
6) <[s40(2)]> - <[s40(2)]> UCLH NHS Foundation Trust
7) <[s40(2)]> – <[s40(2)]>, PHE and <[s40(2)]> NIHR Health Protection Research Unit in Respiratory Infections
8) <[s40(2)]> – <[s40(2)]> Crick Institute
9) <[s40(2)]> <[s40(2)]>, Royal Liverpool University Hospital, and <[s40(2)]> University of Liverpool
10) <[s40(2)]> - <[s40(2)]> University of Glasgow
11) <[s40(2)]>, <[s40(2)]>, North Bristol NHS Trust
12) <[s40(2)]> – <[s40(2)]>, University of Bristol Law School, <[s40(2)]>, UK Faculty of Public Health
13) <[s40(2)]> – <[s40(2)]>, Welsh Government

14) <[s40(2)]> – <[s40(2)]>, Welsh Government
15) <[s40(2)]> – <[s40(2)]>, The Scottish Government
16) <[s40(2)]> – <[s40(2)]>, Department of Health, Northern Ireland
17) <[s40(2)]> - Department of Health, Northern Ireland
18) <[s40(2)]> -<[s40(2)]>, Department of Health & Social Care
19) Professor James Palmer – NHS England and Improvement, National Medical Director, Specialised Commissioning
20) <[s40(2)]> – NHS England and Improvement, <[s40(2)]>, Specialised Commissioning