Cost-effectiveness of Evusheld® (tixagevimab/cilgavimab) for the pre-exposure prophylaxis (PReP) of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of Evusheld® (tixagevimab/cilgavimab). Following assessment of the Applicant's (Astra Zeneca) submission, the NCPE recommends that tixagevimab/cilgavimab (Evusheld®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The HSE asked the NCPE to carry out an evaluation of the Applicant's Health Technology Assessment of Evusheld® (tixagevimab/cilgavimab). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of drugs for cancer the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **December 2022**

Summary

In August 2022, Astra Zeneca submitted a Health Technology Assessment dossier on Evusheld® (tixagevimab /cilgavimab). Tixagevimab and cilgavimab are two recombinant human IgG1κ monoclonal antibodies indicated for pre-exposure prophylaxis (PReP) of COVID-19 in adults and adolescents aged 12 years and older and weighing at least 40 kg. The licensed dose is a single dose of 150mg tixagevimab and a single dose of 150mg cilgavimab, as two injections (one of tixagevimab and one of cilgavimab), given one after the other at different sites. It should be administered intramuscularly in the hospital setting. Of note, the recommended dose is now 300mg of tixagevimab and 300mg of cilgavimab; the increased dose is based on emerging data on effectiveness. In addition to a dose increase, the Applicant now recommends that a further dose at six months is necessary. One pack contains one vial each of tixagevimab 150mg and cilgavimab 150mg. For the purposes of this application, the Applicant has proposed that tixagevimab/cilgavimab be considered as prophylaxis in individuals at risk of inadequate response to a COVID-19 vaccine, or for those for whom a COVID-19 vaccine is contraindicated. This is a sub-population of the licensed indication. It is not intended to replace vaccination for COVID-19.

1. Comparative effectiveness of tixagevimab/cilgavimab

The primary source of evidence, presented in the submission, is the ongoing, phase III, double blind, placebo-controlled PROVENT trial (N= 5,254). This trial assesses the efficacy and safety of a single dose of tixagevimab 150 mg and cilgavimab 150 mg versus placebo. The trial is conducted in an unvaccinated population, recruited at a time prior to the emergence of the Omicron SARS-CoV-2 variant. The predominant SARS-CoV-2 variants, circulating at the time of recruitment, were Alpha, Beta, Gamma, Delta, and Epsilon. Over 70% of the population is considered to have an increased risk of inadequate response to active immunisation (defined by a range of parameters including, for example, being elderly (60 years and over) or being obese (BMI ≥30 kg/m^2)) or having hypertension. Only 3.8% of patients recruited were classified as immunocompromised due to a specific illness or were on immunosuppressive therapy, the population of concern in the current submission. The primary efficacy endpoint is the proportion of patients developing PCR-confirmed symptomatic SARS-CoV-2 illness within 183 days of enrolment. In the event-driven primary analysis, tixagevimab/cilgavimab reduced the risk of PCR-confirmed symptomatic SARS-CoV-

2 illness by 76.7% (95% CI, 46.05 to 89.96: p<0.001) at 3 months (8 events in the tixagevimab/cilgavimab arm compared to 17 events in the placebo arm). The relative risk reduction was 82.8% (95% CI 65.69 to 91.35: p<0.001) at 6 months (11 events in the tixagevimab/cilgavimab arm and 31 events in the placebo arm). Subgroup analyses demonstrated that the efficacy of tixagevimab/cilgavimab was generally consistent across those subgroups with obesity, hypertension or immunosuppressive disease at 6 month follow-up. Of note, there were no, or limited, cases of COVID-19 among certain subgroups (including patients who were immunocompromised) precluding the reliable estimation of respective relative risk reductions. There was no statistically significant difference in the number of participants, in each arm, who presented with severe or critical COVID-19 at 6 months. Health-related quality of life was not investigated.

The Applicant provided evidence from two studies on outcomes from the real world setting. In a retrospective cohort study, a cohort of 1,848 patients, treated with at least one dose of 150mg tixagevimab/150mg cilgavimab, was compared to a cohort of propensity matched controls. The primary outcome was a composite of COVID-19-related hospitalisation and all-cause mortality. After propensity-score matching 1,733 remained in the treatment group and 6,354 in the control group. Estimated from propensity-score matched survival analyses, tixagevimab/cilgavimab recipients had a lower incidence of the composite of COVID-19 outcomes versus control patients overall (17/1733 [1.0%] vs 206/6354 [3.2%]; HR 0.31; 95%CI, 0.18-0.53). This study is associated with a risk of bias arising from factors such as residual confounding and immortal time bias and had a limited duration of follow-up (less than 3 months in most cases). Furthermore, the generalisability of the results to current Irish clinical practice are uncertain in light of differences in circulating variants, patient populations, and healthcare systems.

Further data was presented but was not considered to provide reliable estimates of treatment effectiveness.

2. Safety of tixagevimab/cilgavimab

Safety data for tixagevimab/cilgavimab is derived from PROVENT in addition to the STORM CHASER trial (which evaluated tixagevimab/cilgavimab as prophylaxis after an exposure

event) and the TACKLE trial (which evaluated safety of tixagevimab/cilgavimab as a treatment for COVID-19).

In the PROVENT trial, the frequency of adverse events were similar in the tixagevimab/cilgavimab arm and the placebo arm (41% vs 40% respectively). The most commonly reported adverse events overall were headache, fatigue, and cough across both arms with similar incidence rates. The number of participants with adverse events leading to death were low (0.2% vs 0.3% respectively). The incidence of serious adverse events was low in both arms (2.7% vs 2.4% respectively).

In the on-going TACKLE trial, adverse events were reported in 29% of the tixagevimab/cilgavimab arm compared to 36% in the placebo arm; the majority were mild. There was no difference in the total number of deaths in each arm. The most common adverse event in both arms was COVID-19 pneumonia, also representing the most common serious adverse event. Overall, most adverse events were mild to moderate in severity, while the most common adverse event of special interest was injection site pain.
There was an early signal that the combination of tixagevimab/cilgavimab was potentially associated with an increased risk of thromboembolic events. However, an updated EMA Risk Management Plan states that there are no additional pharmacovigilance activities, clinical measures, or additional risk minimization measures in place.

3. Cost effectiveness of tixagevimab/cilgavimab

A cost-utility analysis was conducted to inform the cost effectiveness of tixagevimab300mg and cilgavimab 300mg relative to placebo (as a proxy for no PrEP). A hybrid decision-tree/Markov health-state transition model was developed in Microsoft Excel® and aligned to the design of PROVENT trial. The population defined in the model comprised adults and adolescents (aged 12 years and above) who were not currently infected with COVID-19, who had not had a known recent exposure to an individual infected with COVID-19 and moderately to severely immunocompromised and may have had an inadequate immune response to COVID-19 vaccination (i.e. a sub-set of the licensed population).

The decision-tree component of the model evaluated costs and health outcomes resulting from acute infection; the Markov component estimated long-term patient costs and health outcomes. Efficacy data was derived from the full-population data from the PROVENT trial; other key model parameters were derived from the literature (including the risk of symptomatic infection, impact of shielding, hospitalisations and probability of developing post-COVID syndrome). The Review Group noted several limitations with the cost effectiveness analyses presented by the Applicant; (i) uncertainty associated with quantifying the target population (ii) the model structure was not appropriate to capture the ongoing risk of COVID-19 infection (iii) the sources of data used to populate the model were derived from literature from early in the pandemic and (iv) sensitivity analyses did not capture the full range of uncertainty associated with the cost-effectiveness of tixagevimab/cilgavimab.

Results

Analyses presented in this document are based on the list prices. An incremental analysis of the costs and benefits of tixagevimab/cilgavimab relative to placebo was provided by the Applicant, the results of which are presented in Table 1 (deterministic). Probabilistic results were similar.

Table 1: Applicant's base case results (deterministic)

Technology	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	ICER (€/QALY)
Tixagevimab/cilgavimab	4,959.41	9.84			
Placebo	691.90	9.74	4267.51	0.10	**44,069**

QALY: Quality Adjusted Life Year; **ICER**: Incremental Cost-Effectiveness Ratio;

*Total costs and QALYs presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

The Review Group considered a number of parameters and assumptions in the Applicant's base case to be problematic or implausible, and concluded that the Applicant's evaluation was insufficient to investigate the true cost effectiveness of this product in this cohort. Most alternative scenarios, considered more or equally plausible by the Review Group, resulted in higher ICERs. The NCPE did not present an adjusted base case, as the following key limitations of the Applicant's cost-effectiveness analysis could not be addressed:

- The model structure does not capture the ongoing risk of COVID-19 infection (and possible reinfection) and its consequences over a lifetime horizon.
- The model does not consider the possibility of treatment with tixagevimab/cilgavimab continuing beyond 1 year.
- Treatment effectiveness in the model is based upon prevention of symptomatic infection, as observed in PROVENT. The generalisability to the target population, current and future SARS-CoV-2 variants, and across different levels of COVID-19 severity, are all unknown.
- The model population is highly heterogeneous, and it is not necessarily the case that costs and outcomes for the mean patient (as considered in the model) will be reflective of mean costs and outcomes across the target population.

In order to inform on the uncertainty in the cost-effectiveness of tixagevimab/cilgavimab in the target population additional sensitivity and scenario analyses were undertaken by the Review Group.

Sensitivity and Scenario analyses

In order to highlight some of the parameter uncertainty in the model, the Review Group ran a number of additional scenario analyses, which, in a number of instances apply equally plausible assumptions, but which were not shown/considered by the Applicant. The first scenario consisted of two 'baseline' changes, to the starting age of the cohort and a re-calculation of infection rates (to account for shielding), intended to apply more realistic assumptions. This resulted in an ICER of €67,946/QALY. All other scenarios were additional to these two baseline changes and resulted in ICERs ranging from €35,681/QALY to €136,272/QALY.

In general, the results indicated that tixagevimab/cilgavimab appeared to be more cost-effective in scenarios where:

- Efficacy observed in PROVENT is applicable to the target population and circulating variants, particularly against severe outcomes
- Baseline infection risk, and/or hospitalisation risk following infection, is high in the target population
- Many patients would otherwise be shielding

- Long-term non-COVID mortality is low.

However, the Review Group emphasise that none of these scenarios can fully explore the range of plausible long-term scenarios regarding COVID-19 mortality, morbidity, and healthcare costs in patients who are immunocompromised, including the possibility that PrEP with tixagevimab/cilgavimab may be administered beyond year 1.

4. Budget impact of tixagevimab/cilgavimab

The price to wholesaler of one vial of 150mg tixagevimab and 150mgcilgavimab is €1,093 (excl. VAT).

The total cost of one 600mg dose of tixagevimab/cilgavimab to the HSE is €2,688.78 (incl. VAT 23%) and €2,186 (excl. VAT). The total cost per patient per year is €5,377.56 (incl. VAT) and €4,372 (excl. VAT). Using the population estimates for eligible population identified by the Applicant, this resulted in a gross drug budget impact of €103.5 million (incl. VAT) in year one and €105.1 million (incl. VAT) in year two. The net drug budget impact was equal to the gross drug budget impact as PrEP treatment represents a new addition to the treatment paradigm. The Review Group noted that the population estimates provided by the Applicant were based on a narrower group of patients compared to the cohort identified for the cost effectiveness analysis, therefore the results of the budget impact analyses are highly uncertain.

5. Patient Organisation Submissions

No Patient Organisation Submissions were received during the course of this assessment.

6. Conclusion

The NCPE recommends that tixagevimab/cilgavimab not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.