Cost-effectiveness of osimertinib (Tagrisso®) for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC)

The NCPE assessment of osimertinib has demonstrated additional benefit in progression-free survival (PFS) and some evidence of benefit in overall survival (OS), though the size of the OS gain is very uncertain due to the high level of treatment switching in the comparator arm of the pivotal trial. There is a very low probability of cost effectiveness and a high probability that the ICER far exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that osimertinib (Tagrisso®) 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 National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Astra Zeneca Pharmaceuticals (Ireland) DAC) economic dossier on the cost effectiveness of osimertinib (Tagrisso®). The NCPE uses a decision framework to systematically assess whether a technology is clinically effective and 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 cancer drugs 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 **May 2018**

In March 2017, Astra Zeneca Pharmaceuticals (Ireland) DAC submitted a dossier of clinical, safety and economic evidence in support of osimertinib, for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC). A resubmission with additional evidence was received in January 2018. Osimertinib is a tyrosine kinase inhibitor (TKI) and an irreversible inhibitor of EGFR harbouring sensitising-mutations and TKI-resistance mutation T790M. The recommended dose of osimertinib is 80 mg once daily taken orally until disease progression or unacceptable toxicity. It is anticipated that osimertinib will primarily be used as second line (2L) treatment in patients who have disease progression following first line treatment with a first- or second-generation EGFR-TKI.

1. Comparative effectiveness of osimertinib

- The comparator for osimertinib is current standard of care which consists of platinum-doublet chemotherapy (PDC). The AURA3 study was a pivotal phase III, open-label, comparative, randomised study conducted in 419 patients with advanced EGFR T790M mutation-positive NSCLC in second-line therapy versus PDC. There was a statistically significant improvement in progression-free survival (PFS) for patients on osimertinib compared to patients on chemotherapy (10.1 months vs 4.4 months, +5.7 months, HR 0.30, 95% CI: 0.23, 0.41 p<0.001). The immaturity of the data (26.0%) at the time of the first overall survival (OS) analysis prevents firm conclusions on the benefits of osimertinib in improving survival (immature HR 0.72, 99.96% CI 0.34, 1.52). A high level of treatment-switching (67.1% crossover) from PDC to osimertinib after progression also confounds interpretation of results.
- An initial submission of evidence supporting comparative efficacy in OS applied adjusted indirect comparison methodology to pooled single arms of osimertinib phase II studies, and the control arm of a phase III study containing PDC. The NCPE review group considered the AURA3 study, adjusted for crossover, to be the most appropriate source of OS data for use in the cost-effectiveness model, as it directly addresses the clinical aspect of the decision problem in the target population, without the need for subset-selection, matching, trimming and indirect comparison. The applicant submitted results of OS analysis based on AURA3 (data cut-off 2, DCO2) adjusted for crossover in the January 2018 resubmission, and updated this with data from AURA3 (DCO3) in March 2018. The updated analysis used the rank-preserving

structural failure time (RPSFT) model to adjust the OS of patients who crossed over from PDC to osimertinib, and presented results based on various methodologies. The adjusted OS HR estimates ranged from [redacted] to [redacted] This analysis was updated on request from the NCPE on the basis of more mature data from AURA3 DCO3. The adjusted HR estimates on the basis of this update ranged from to Notwithstanding the provision of the AURA3-DCO3 OS results adjusted for crossover, as requested by the NCPE review group, there remains no robust evidence of an overall survival advantage with osimertinib to support the applicant's model.

2. Safety of osimertinib

- Overall, the safety profile of osimertinib appears better than that reported for PDC within the AURA3 study. There were less AEs grade 3 or higher (regardless of causality), serious AEs and AEs leading to discontinuations. The profile of AEs of osimertinib is mainly characterised by diarrhoea (40.5%); dry skin (18.6%); decreased appetite (17.9%); paronychia and cough (16.5% each); nausea (16.1%); and fatigue (15.8%). Most adverse reactions to osimertinib were Grade 1 or 2 in severity. Grade ≥ 3 were more frequently reported in the chemotherapy arm (22.6% vs 47.1%).

3. Cost effectiveness of osimertinib

Methods

- A cost-utility analysis, comparing osimertinib with PDC in the second-line treatment setting from the perspective of the Irish Health Services Executive, was submitted by the applicant. The analysis utilised a partitioned-survival model including three health states; progression free, progressed disease, and death to model costs and benefits of treatment over a lifetime horizon. PFS outcomes were based on DCO1 of the AURA3 study and OS outcomes were based on crossover-adjusted analysis of DCO3 of the AURA3 study, extrapolated over a lifetime horizon using parametric extrapolation. An independent model approach was selected to generate the osimertinib OS curve from AURA3 (DCO3). The PDC curve was generated by applying the inverse of the adjusted HR to the osimertinib curve using a proportional hazards approach. The OS data was extrapolated over the time horizon of the model using parametric modelling. The difference in statistical fit between the best-fitting models was not indicative of any substantial difference in actual goodness-of-fit. The median estimated OS

durations were similar across models, consistent with a similar fit to the short-term observed data. However the mean osimertinib OS durations predicted by each of these models varies significantly, from 31.76 months with the weibull model (most conservative) to 43.09 months with the log-normal model (least conservative). The applicant's chosen models for long-term extrapolation of OS and PFS benefits predict a survival advantage of 18.92 months for osimertinib compared with PDC. Survival benefits were predicted to continue for over 2 years after disease progression and also for almost 22 months after patients are assumed to have discontinued treatment. The NCPE has concerns regarding the mean OS predicted by the model and consequently the extent of OS benefit predicted.

- The primary health outcome of the model was the quality adjusted life year (QALY) as per national guidelines. Resources were estimated by a key external expert engagement exercise conducted by the applicant, and included drug acquisition, administration and monitoring costs (including adverse events), and disease management costs. Health-related quality of life (HRQoL) utilities were applied to the three model health states and utility decrements due to grade 3/4 adverse events were also included. Utility values were derived from the AURA3 study. The HRQoL of the very select clinical trial population may not be representative of the cohort of patients eligible for treatment. This is reflected in the very high values for the progression free state (0.823) and the progressed disease state (0.727). The progression free utility value lacks face validity as it is higher than the EQ-5D-3L index population norm for people of the same age.

Results

- The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the applicant's base case was €116,785/QALY. The probability of cost-effectiveness at a willingness to pay threshold of €45,000/QALY was 0%. The NCPE did not consider that the applicant's submitted model and resulting ICER are a complete reflection of the cost effectiveness of osimertinib, and explored the impact of alternative utility values, treatment durations and treatment efficacy estimates on cost effectiveness results. The NCPE implemented a number of changes to the model based on plausible alternative assumptions, resulting in increases in the ICER up to €241,953/QALY. This ICER still reflects the potential for an OS benefit with osimertinib. If the

assumed OS advantage with osimertinib is removed, the ICER increases to over €1.5 million/QALY.

4. Budget impact of osimertinib

- Osimertinib is submitted for reimbursement under the High-tech drug scheme. The proposed ex-manufacturer price is €6200 for 30 tablets. The reimbursement cost for a treatment course is dependent on treatment duration, which is patient-specific depending on response and tolerance, but on the basis of current evidence could range from an average of €121,058 to [redacted] per patient. Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €24.9 million, plausibly increasing to over €30 million if treatment durations are longer. The uptake of osimertinib is assumed to displace the use of PDC in the 2L setting. Given the relatively low costs of PDC, the net savings are also very low, of the order 4% to 5%.

5. Conclusion

- The NCPE assessment of osimertinib has demonstrated additional benefit in PFS and some evidence of benefit in OS, though the size of the OS gain is very uncertain due to the high level of treatment switching in the comparator arm of the pivotal trial. There is a very low probability of cost effectiveness and a high probability that the ICER far exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that osimertinib (Tagrisso®) 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.