Cost-effectiveness of osimertinib (Tagrisso®) for the first-line treatment of adult patient with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations.

The NCPE has issued a recommendation regarding the cost-effectiveness of osimertinib (Tagrisso®). Following assessment of the applicant's submission, 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 (AstraZeneca) economic dossier on the cost effectiveness of osimertinib (Tagrisso®). 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 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 **August 2019**

Summary

In January 2019, AstraZeneca submitted an economic dossier examining the cost effectiveness of osimertinib (Tagrisso®) for the first-line treatment of adult patients with epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI). It is an irreversible inhibitor of EGFRs harbouring sensitising mutations and TKI resistance mutation T790M, leading to inhibition of cell growth.

The recommended dose of osimertinib is 80mg once daily until disease progression or until unacceptable toxicity. If a dose reduction is necessary, then the dose should be reduced to 40 mg once daily. Osimertinib is formulated as 40mg and 80mg film coated tablets.

The main comparators are the EGFR-TKIs erlotinib, afatinib and gefitinib. This was considered appropriate by the Review Group and is in line with the current standard of care in Ireland.

1. Comparative effectiveness of osimertinib

The FLAURA study was a phase III, double-blind, randomised study assessing the efficacy and safety of osimertinib vs. standard of care (SoC) as first line treatment in patients with EGFR mutation-positive locally advanced or metastatic NSCLC. Patients (N=556) were randomised in a 1:1 ratio to receive either osimertinib 80mg once daily or a choice of either gefitinib 250mg once daily or erlotinib 150mg once daily. Efficacy was investigated in the intent-to-treat population. There was a statistically significant improvement in progression free survival (PFS) for patients on osimertinib compared to patients on SoC. The median PFS with osimertinib was 18.9 months (95% CI 15.2 to 21.4) compared to 10.2 months (95% CI 9.6 to 11.1) with SoC. At time of analysis the overall survival (OS) data was immature (25.4% events had occurred), preventing firm conclusions on the benefits of osimertinib in improving survival. There was a high degree of crossover from SoC to osimertinib (upon progression). Efficacy outcomes (and thus cost-effectiveness) were not adjusted for this.

Health related quality of life was measured via the EORTC QLQ-C30 and EORTC QLQ-LC13 instruments.

The Applicant conducted an indirect treatment comparison to generate estimates of relative efficacy to afatinib. However, the Applicant did not apply the results of the indirect treatment comparison in the cost-effectiveness model. Instead the Applicant assumed equal efficacy to erlotinib and gefitinib. The Review Group have concerns that this approach may bias the model in favour of osimertinib.

2. Safety of osimertinib

The safety review of osimertinib was primarily based on the results of the FLAURA trial (N=556). No new safety signals were detected. The safety profile of osimertinib appears similar to that of SoC. Osimertinib had a more favourable profile regarding the severity of adverse events with a lower frequency of adverse events Grade ≥ 3 causally related to the treatment. Adverse Events of special interest include: interstitial lung disease/ pneumonitis, cardiac effects (QT and cardiac failure), diarrhoea, skin effects, upper gastrointestinal inflammatory events, nail effects, ocular effects, renal effects, hepatobiliary effects and infections/infestations. Overall osimertinib was at least as well tolerated as SoC. No comparative safety information with afatinib was provided.

3. Cost effectiveness of osimertinib

For the cost-effectiveness analysis, the effectiveness inputs in the model were PFS, OS and time to treatment discontinuation. Cost-effectiveness was investigated using a three health state model with a 20 year time horizon. The model simulated patients through three health states: 'Progression-free', 'Progressive disease' and 'Death'. All patients started in the progression-free state; transitions to the death state could occur from either progression-free state or progressive disease states. Patient characteristics, adverse event frequency and utility measurements were derived from the FLAURA trial. The Applicant mapped EORTC QLQ-C30 outcomes from FLAURA to EQ-5D-3L to produce health state utility values. Disutilities were applied for adverse events based on values obtained from literature. Costs were included in the model for disease management, drug administration, drug acquisition, drug monitoring, subsequent treatments (including cost of T790M mutation testing),

adverse events, and costs due to central nervous system metastases. Upon progression, patients treated with osimertinib were subsequently treated with platinum doublet chemotherapy. Patients on SoC subsequently received either osimertinib or platinum doublet chemotherapy.

The Applicant excluded gefitinib from the model, as its market share was considered low. Relative efficacy of osimertinib vs. erlotinib is derived from the FLAURA study. The model assumes that afatinib has equal efficacy to erlotinib.

Survival outcomes from FLAURA were extrapolated to the full time horizon of the model using parametric extrapolation. For extrapolation of OS the Applicant chose a piecewise model up to 7.9 months, followed by a Weibull model. Given the immaturity of the OS data, there is considerable uncertainty surrounding the most appropriate method to model OS. Therefore, the Review Group updated the model choosing the most conservative approach, the fully parametric Weibull distribution. Furthermore, there is considerable uncertainty associated with the time to treatment discontinuation extrapolation assumptions in the model. The model is highly sensitive to choice of curve.

Results

The Review Group implemented a number of changes to the model including the choice of parametric curves and updating the maximum number of platinum doublet chemotherapy cycles to six. The resultant NCPE preferred base case ICERs are €115,912 per QALY (incremental cost/incremental QALY €78,556/0.678) vs. erlotinib and €113,162 per QALY (incremental cost/incremental QALY €76,693/0.678) vs. afatinib. In the Applicant base case, the incremental cost-effectiveness ratio (ICER) was €78,914 per QALY (incremental cost/ incremental QALY €75,818/0.961) vs. erlotinib and €76,975 per QALY (incremental cost/ incremental QALY €73,954/0.961) vs. afatinib.

Using the NCPE preferred base case, at a cost-effectiveness threshold of €20,000 and €45,000 per QALY the probability of cost-effectiveness is 0%.

4. Budget impact of osimertinib

Osimertinib is submitted for reimbursement under the High Tech Drug Arrangement. The price to wholesaler of osimertinib is €6,200 for 30 tablets. The treatment cost per patient is dependent on treatment duration. The budget impact presented is the mean treatment duration based on time to treatment discontinuation extrapolation in the cost-effectiveness model. The Review Group made a number of changes to the Applicant's budget impact model including: application of a full 5-year budget impact, market share and patient eligibility. Under these assumptions it is estimated that 36 patients will be eligible for treatment with osimertinib in year one increasing to 87 patients in year five. The resultant 5-year cumulative gross budget impact is estimated to be €50.23million. The cumulative 5-year net budget impact is estimated to be €39.34million. Using the Applicant estimates, the 5-year cumulative gross budget impact is €25.88million and the 5-year net budget impact is €20.09million. The Review Group highlight that there is uncertainty associated with the estimates of the eligible number of patients and market share, but consider that the Applicant has likely underestimated the budget impact.

5. Patient submissions

No patient organisation submissions were received during the course of this appraisal.

6. Conclusion

Following assessment of the Applicant's submission, 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.