Cost Effectiveness of Pertuzumab (Perjeta®) in Combination with Trastuzumab and Docetaxel in Adults with HER2-Positive Metastatic or Locally Recurrent Unresectable Breast Cancer Who Have Not Received Previous Anti-HER2 Therapy or Chemotherapy

The NCPE has issued a recommendation regarding the use of pertuzumab for this indication. The NCPE do not recommend reimbursement of pertuzumab.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to evaluate the manufacturers (Roche Products Ltd) economic dossier on the cost effectiveness of pertuzumab. 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 examine 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 2013**

Summary

1. In May 2013 Roche Products (Ireland) Limited submitted an economic evaluation to the National Centre for Pharmacoeconomics (NCPE). The basecase analysis evaluates the cost effectiveness of pertuzumab + trastuzumab + docetaxel compared to trastuzumab + docetaxel in adults with HER2-positive metastatic breast cancer (mBC) or locally recurrent unresectable breast cancer (LRBC), who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. The perspective of the economic evaluation is that of the Health Service Executive. The drug is eligible for reimbursement as a hospital-only product. Efficacy and safety data was obtained from the CLEOPATRA (CLinical Evaluation Of Pertuzumab And TRAstuzumab) study [1].

2. CLEOPATRA was a phase III clinical study which investigated the use of pertuzumab in the first-line treatment of patients with HER2-positive mBC [1]. Eight hundred and eight patients (from 204 centres across 25 countries) were randomly assigned (1:1) to receive pertuzumab (840 mg in cycle 1; 420 mg every three weeks in subsequent cycles) + trastuzumab (8 mg/kg in cycle 1; 6 mg/kg every three weeks in subsequent cycles) + docetaxel (75 mg/m^2 escalating to 100 mg/m^2 IV every three weeks) (the Pertuzumab group) or to receive placebo + trastuzumab + docetaxel (the Control group). Treatment was continued until the time of disease progression or the development of toxic effects that could not be effectively managed.

   The primary end point was independently assessed progression-free survival (PFS). Secondary end points included overall survival (OS), PFS as assessed by the investigator, objective response rate (ORR), and safety. Efficacy endpoints were analysed in the intention-to-treat (ITT) population and safety was analysed by treatment received. Median follow-up was 19.3 months in both groups.

   The estimated median duration of study treatment was 11.8 months and 18.1 months in the Control and Pertuzumab groups respectively. Median independently assessed PFS was 12.4 months and 18.5 months in the Control and Pertuzumab groups respectively (Hazard Ratio (HR) for progression or death =

0.62, 95% CI 0.51-0.75; p<0.001). Interim analysis of OS was performed after 165 events (43% of the prespecified total number) had occurred (data cut-off: May 2011). More deaths occurred in the Control group (23.6% vs. 17.2%); this was not statistically significant. ORR in the Control and Pertuzumab groups were 69.3% and 80.2% respectively.

Higher rates of diarrhoea, rash, mucosal inflammation, pruritis, febrile neutropenia and dry skin (all grades) of at least 5% were reported in the Pertuzumab group [1].

After an additional year of follow-up (cut-off: May 2012; median follow-up in both groups = 30 months), 38% and 28% of the Control and Pertuzumab groups respectively had died. Median OS was 37.6 months in the Control group and had not been reached in the Pertuzumab group (HR= 0.66, 95% CI 0.52-0.84; p=0.0008). Median investigator-assessed PFS was 12.4 months and 18.7 months in the Control and Pertuzumab groups respectively (HR= 0.69, 95% CI 0.58-0.81). Independently assessed PFS data was not gathered during this additional year of follow-up. [2].

3. The company presented an area under the curve (AUC) model, developed in Microsoft Excel®. The model has three mutually exclusive health states: 'PFS', 'Progression' and 'Death'. The time horizon is 15 years.

   The probability of patients remaining in the PFS health state is determined by probabilities obtained from the CLEOPATRA Kaplan-Meier (KM) estimates (cut off: May 2012) [1] or from a log-logistic function fitted to this KM data. Four additional extrapolation possibilities were included. These were intended to facilitate the exploration of changes in the rate of disease progression. Following the selection of either the parametric functions or KM curves with the parametric extrapolation, the basecase evaluation employs a 'No Piecewise Exponential'.

   The probability of being alive was determined by OS probabilities obtained from the study KM estimates (cut off: May 2012) or from a fitted parametric function. The patients surviving in the tails of the curves were then modeled using the

similar constant hazards of death from the Munich Tumour Registry [3]. After a time period of 50 months, the remainder of patients still alive were exposed to the rate of death observed from 64 patients followed up in this registry (estimated by the Weibull function). The proportion of patients in the 'Progression' health state is assumed to be the difference between the number of patients in 'PFS' and 'Death' states.

4. In the basecase economic analysis, pertuzumab + trastuzumab + docetaxel resulted in ICERs of €162,857/LYG and €203,028/QALY when compared to trastuzumab + docetaxel. This analysis assumes that vials will be shared (i.e. there will be no drug wastage). In reality, unused drug is likely to be wasted. When this is assumed, the ICER increases to €206,720/QALY.

5. The ICER is also sensitive to a number of key assumptions:

- the ICER ranges from €137,219/QALY to €210,460/QALY depending on the assumed OS parametric distribution
- the ICER ranges from €202,968/QALY to €221,846/QALY depending on the assumed PFS parametric distribution
- the ICER increases to €288,486/QALY when the time horizon is decreased to 5 years
- the ICER increases to €236,677/QALY when it is assumed that treatment will continue until the time of disease progression
- the ICER increases to €253,785/QALY when all the health state utilities are decreased by 20%. This sensitivity is important considering that disease specific quality of life data (FACT-B) was collected in CLEOPATRA and was not used in this economic evaluation, nor was it made available to the NCPE.

6. A probabilistic analysis is presented. At a threshold of €45,000/QALY, there is a 2.5% probability that pertuzumab is cost effective.

7. The median treatment duration of pertuzumab in the CLEOPATRA trial was about 18 months [1]. An 18 month course of treatment will cost about €74,000 per patient at the price currently being sought for pertuzumab.

8. The budget impact analysis (BIA) was performed over a 5-year time horizon assuming reimbursement as a hospital-only product. In this BIA it is assumed there is an incidence of 130 first line HER2-positive MBC patients in Ireland in 2013. We assume that there will be no vial sharing (i.e. unused drug will be wasted). If it is assumed that each Year (1-5) comprises of a 12 month period, the gross pertuzumab budget impact might increase from about €6.04 million in Year 1 to about €9.83 million in Year 5 (cumulative ~ €39.37 million).

9. In conclusion, pertuzumab significantly increases median progression free survival for patients with HER2-positive mBC. Although overall survival is improved, a true estimate of this gain is uncertain at this point in time. Pertuzumab is an expensive drug which can be expected to result in an additional treatment cost of approximately €74,000 per patient and an estimated gross budget impact of about €39 million over the next five years. With a basecase ICER of €203,028/QALY (or €162,857/LYG) the manufacturer has failed to demonstrate that pertuzumab is cost effective in the Irish Healthcare Setting.

   The NCPE believes that pertuzumab is not cost effective at the submitted price and we cannot recommend reimbursement. A significant price reduction is required to ensure value for money.

References

1. Baselga J, Cortes J, Kim S-B, Im S-A, Hegg R, Im Y-H, et al. For the CLEOPATRA Study Group. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. N Eng J Med 2012;366(2):109-119.
2. Swain SM, Kim S-B, Cortés J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. The Lancet Oncology 2013;14(6):461-471.
3. Tumorregister-Muechen 2012 (http://www.tumorregister-muenchen.de/fehler404.htm).