Cost-effectiveness of pertuzumab (Perjeta®) (in combination with trastuzumab and chemotherapy) for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of pertuzumab (Perjeta®) (in combination with trastuzumab and chemotherapy). Following NCPE assessment of the Applicant's submission, pertuzumab (Perjeta®) is not considered cost effective for the treatment of this indication and therefore is not recommended for reimbursement.

The HSE asked the NCPE to carry out an assessment of the applicant's (Roche Products Ireland Ltd) economic dossier on the cost effectiveness of pertuzumab (Perjeta®) (in combination with trastuzumab and chemotherapy). 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 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 2016**

Summary

In November 2015, Roche Products Ireland Ltd submitted a dossier to examine the cost effectiveness of pertuzumab (Perjeta®) (in combination with trastuzumab and chemotherapy) for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. It is anticipated that pertuzumab will be used (with trastuzumab + chemotherapy) as a first line treatment for this indication.

1. Comparative effectiveness

NeoSphere was a multicentre, open-label, phase II study in treatment-naive women (n=417) with HER2-positive breast cancer. Patients were randomly assigned (1:1:1:1) to receive four neoadjuvant cycles of: trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) + docetaxel (75 mg/m^2, escalating, if tolerated, to 100 mg/m^2 every 3 weeks (TD; n=107)) or pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks) + trastuzumab + docetaxel (PTD; n=107) or pertuzumab + trastuzumab (PT; n=107) or pertuzumab + docetaxel (PD; n=96). The primary endpoint was post-surgery pathologic complete response in the breast (bpCR) in the intention-to-treat population. Patients on PTD had a significantly improved bpCR rate (45.8%; 95% CI 36.1-55.7) vs. those on TD (29.0%; 95% CI 20.6-38.5; p=0.0141). The bpCR rate was 24.0%; 95% CI 15.8-33.7 in those on PD (comparable to TD). The bpCR rate was 16.8%; 95% CI 10.3-25.3 with PT. The secondary endpoints of progression free survival (PFS) and disease free survival were evaluated at 5 years after randomisation. The study was not designed to show statistical significant for these endpoints.

The Review Group notes that all patients received four treatment cycles in NeoSphere. The SmPC for pertuzumab states that pertuzumab (with trastuzumab +chemotherapy) should be continued for 3 to 6 cycles for this indication. Further, in NeoSphere, FEC chemotherapy (fluorouracil, epirubicin, cyclophosphamide) was given after surgery. In reality, FEC or another anthracycline-based chemotherapy would be given prior to surgery.

2. Safety

In NeoSphere, the most common Grade ≥ 3 adverse events were neutropenia: 61/107 (TD arm), 48/107 (PTD arm), 1/108 (PT arm), and 52/94 (PD arm), febrile neutropenia (eight,

nine, none, and seven, respectively), and leucopenia (13, five, none, and seven, respectively). The number of serious adverse events was similar in the TD, PTD and PD arms (15-20 serious adverse events per group in 10-17% of patients) but lower in the PT arm (four serious adverse events in 4% of patients). There was a greater than 5% incidence rate with diarrhoea (45.8% (PTD) vs. 33.6% (TD)), rash (40.2% (PTD) vs. 29.0% (TD)) and mucositis (45.8% (PTD) vs. 33.6% (TD)).

TRYPHAENA was a phase II, open-label, randomised, multinational, multicentre trial in patients with early and advanced HER2-positive breast cancer The trial was designed to evaluate tolerability, particularly with respect to cardiac function, associated with trastuzumab and pertuzumab based chemotherapy regimens. A total of 225 patients were enrolled and randomised to receive: Flourouracil + epirubicin + cyclophosphamide + trastuzumab + pertuzumab (3 cycles) followed by pertuzumab + trastuzumab + docetaxel (3 cycles) PT+FEC/PTD) (n=73) or FEC (3 cycles) followed by pertuzumab + trastuzumab + docetaxel (3 cycles) (FEC/PTD) (n=75) or pertuzumab + trastuzumab + carboplatin + docetaxel (P+TCD) (6 cycles) (n=77). During neoadjuvant treatment, two patients on FEC/PTD (2.7%) experienced symptomatic left ventricular systolic dysfunction and four patients (5.6%) on PT+FEC/PTD, four patients (5.3%) on FEC/PTD, and three patients (3.9%) on P+TCD experienced left ventricular ejection fraction declines of ≥10% points from baseline to <50%. It was concluded that the incidence of these cardiac events was similar across arms.

3. Cost effectiveness

Within the submission, the Applicant presents Local Expert Opinion which identified ACTH (doxorubicin, cyclophosphamide, taxane, trastuzumab) or TCH (taxane, carboplatin, trastuzumab) given in advance of surgery as the standard of care in Ireland. The Applicant performed a systematic literature review of randomised controlled trials of all pharmacological treatments used in the treatment of HER2-positive breast cancer. The Applicant investigated the feasibility of conducting meta-analyses. It was concluded that there was no data available to compare the current standard of care and it was not possible to generate evidence for other comparators. The only comparator considered in the cost-effectiveness evaluation is trastuzumab + docetaxel (i.e. a comparator in NeoSphere). The NCPE Review Group believes that this cost-effectiveness analysis considers an inappropriate

comparator. As informed by NeoSphere, patients in both arms of the model receive three cycles of FEC and an additional 13 cycles of trastuzumab (total of 17 cycles). This use of FEC is not confirmed by Local Expert Opinion.

Methods

The cost-effectiveness analysis uses a probabilistic six state transition Markov model constructed in Microsoft Excel® with a life-time time horizon and a monthly cycle length. The model consists of six health states: 'event free survival', 'locoregional recurrence' 'remission', 'metastatic (not progressed)', 'metastatic (progressed)' and 'death'. The perspective is that of the Health Service Executive; only direct healthcare costs are considered.

In NeoSphere, tpCR (defined as absence of invasive residuals in the breast and axillary lymph nodes) was a secondary endpoint measured just once at 12 weeks of treatment in both arms. In this analysis, tpCR is the key effectiveness input chosen for the cost-effectiveness model; it is employed to be a surrogate for event free survival. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) analysis was a pooled analysis of 12 international trials that sought to establish the association between pathologic complete response and a number of outcomes including event free survival. This cost-effectiveness analysis uses the tpCR rates observed in NeoSphere in combination with the event free survival rate for tpCR and no tpCR from the CTNeoBC analysis. The NCPE Review Group notes that pathologic complete response is not a validated surrogate endpoint for event free survival. The cost-effectiveness analysis uses parametric extrapolations of the survival Kaplan Meier data from the CTNeoBC analysis. The Gamma function was considered the best fit. Alternative curves are explored in sensitivity analysis. Parametric functions are used to estimate the first 10 years of event free survival. It is assumed that after 10 years the treatment effect in both arms is equal; this is uncertain. Alternative time points for treatment effect equal are explored in sensitivity analysis.

Transition from 'event free survival' to 'metastatic (not-progressed)' or 'locoregional' is based upon the TD and PTD arms of NeoSphere. Across the arms, 58% of disease progression observed was progression to the metastatic health state and the remaining 42% were locoregional. The absolute disease progression rates in both arms are unclear. All

patients experiencing locoregional recurrences receive 12 months treatment with trastuzumab with 7 cycles of chemotherapy (assumed to be docetaxel) and then enter remission. The model assumes that if a patient progresses to metastatic disease, the transition probabilities, treatment and costs are the same irrespective of prior treatment. Transition probabilities of moving from 'metastatic (not-progressed)' to 'metastatic (progressed)' and the transition probability of moving from 'metastatic (progressed)' to 'death' were derived from CLEOPATRA. CLEOPATRA was a randomised, double-blind, placebo-controlled, multicentre phase 3 study that investigated efficacy of pertuzumab + trastuzumab + docetaxel versus placebo + trastuzumab + docetaxel in HER2-positive metastatic breast cancer. In the model, people can transition into the 'death' state from all stages of the model except the 'locoregional recurrence' state (12 month tunnel). Excluding a transition to 'death' here will overestimate the number of people who remain in this state.

A utility value was assigned for each health state except 'death'. Disutilities for adverse events were not included. We believe that it is unreasonable to assume that Grade ≥3 adverse events such as alopecia, diarrhoea, febrile neutropenia, leukopenia and neutropenia will not be associated with a decrement in health related quality of life.

Drug dosages and treatment duration follow those in NeoSphere; it is assumed that all patients receive four cycles of treatment. It is assumed that vials will not be shared. Aseptic compounding costs are not included. Administration costs are included. It is assumed that monitoring of left ventricular ejection fraction during treatment will be with ECG. The Review Group requested that a weighted average cost of ECG, MUGA and MRI be used instead; this change was not made. It is assumed that patients who develop leukopenia will receive treatment with GCSF; GCSF is not licensed for this indication. The model assumes that patients who develop neutropenia will receive treatment with GCSF. In reality in Ireland, GCSF is used to prevent neutropenia in patients at risk, rather than to treat established neutropenia.

Costs are applied to each health state except 'death'. Market research carried out in 2013 was used to derive key resources used in the treatment of patients with metastatic breast cancer. The Review Group conclude that the resultant cost/resource assumptions for the metastatic stages are unrealistically high and that the resultant model will be associated with a degree of bias. Cardiac monitoring of patients on primary treatment is minimal, but almost all patients

are expected to require CT or MRI/ECG/ECHO four times a year in the post progression stages. In the original model, patients had no consultant visits whilst on treatment and 7.5 per annum in the post progression stages. The Applicant amended the base case to include 4 visits based on the responses from the resource use questionnaire. Also, patients are assumed to have a full blood test every month and nine tumour marker blood tests per annum in the post progression states. The Review Group requested that these costs be reviewed; the Applicant believed the costs to be appropriate and changes were not made. The Applicant does acknowledge that the model may overestimate costs at the very end of a patient's life. Costs of treating Grade ≥ 3 adverse events that occurred in ≥5% of patients during the first year of treatment in either arm in NeoSphere are included.

Results

According to the Applicant's assumptions, the cost-utility incremental cost-effectiveness ratio (ICER) for pertuzumab (+ trastuzumab + docetaxel) versus trastuzumab (+ docetaxel) is €9,365/QALY (incremental cost = €2,490; incremental QALY =0.27). The probabilistic ICER is €9,981/QALY. The cost-effectiveness ICER is €8,252/LYG (incremental cost = €2,490; incremental LYG = 0.30). The probabilistic ICER is €8,780/LYG. However, these ICERs are based upon a comparison with trastuzumab + docetaxel; we consider the comparator to be inappropriate. The analysis also employs tpCR as a surrogate for improved event free survival; this is not a validated surrogate endpoint for this outcome. The ICERs assume that all patients will receive four cycles of treatment; the SmPC states that pertuzumab (+ trastuzumab + chemotherapy) should be given for three to six cycles for this indication. The results further assume that FEC would be given after surgery; this does not reflect practice in Ireland.

Sensitivity analysis

Sensitivity analyses indicate that the key drivers for the model are the pathologic complete response rates for both treatment arms, the number of treatment cycles, the time point for treatment effect equal and the discount rate applied to costs and effects. An alternative structural approach uses the five-year event free survival data which was collected in NeoSphere as an exploratory endpoint. This data was extrapolated using parametric methods. The resultant ICER varied with parameter distribution, from dominant (LogNormal) to

€19,900/QALY (Exponential). Event free survival data was an exploratory endpoint in NeoSphere; this structural sensitivity analysis is uncertain.

4. Budget impact

Pertuzumab is available as a 420mg vial at €2,761.65. In the budget impact model, all regimens are costed for four cycles, vial sharing is assumed not to occur and a patient weight of 72kg is assumed. Aseptic compounding and administration costs are not included. Under the Applicant's assumptions, the per-patient treatment cost of pertuzumab is estimated to be €16,984. The 5 year cumulative gross budget impact of the addition of pertuzumab to ACTH and TCH regimens will be about €18.63 million. The Review Group estimates that this impact will increase to about €26.83 million if it is assumed that all patients will receive 6 cycles of treatment. Further, in the extreme, if uptake were to approach 100% it would be about €40.06 million. Under the Applicant's assumptions, the 5 year cumulative incremental budget impact will be about €11.42 million. The Review Group estimates that if all patients receive 6 cycles of treatment, this 5 year impact might be about €16.0 million, increasing to about €23.9 million at 100% uptake.

5. Conclusion

Following NCPE assessment of the Applicant's submission, cost effectiveness of pertuzumab (Perjeta®) (in combination with trastuzumab and chemotherapy) for this indication has not been demonstrated. Therefore it is not recommended for reimbursement. The cost-effectiveness analysis employs an unrealistic comparator and treatment pathway. The analysis uses tpCR (measured just once at 12 weeks of treatment in both arms in NeoSphere) as a surrogate outcome for improved event free survival. tpCR is not a validated surrogate for this outcome. The base case assumes that all patients will receive four cycles of treatment.