Cost effectiveness of Pertuzumab (Perjeta®) for use in combination with trastuzumab and chemotherapy, for the adjuvant treatment of adult patients with HER2-positive breast cancer at high risk of recurrence

The NCPE has issued a recommendation regarding the cost effectiveness of pertuzumab (Perjeta®) (in combination with trastuzumab and chemotherapy). Following assessment of the applicant's submission, the NCPE recommends that pertuzumab (in combination with trastuzumab and chemotherapy) 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 (Roche Products Ireland Ltd) economic dossier on the cost effectiveness of Pertuzumab (Perjeta®). 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 **January 2019**

Summary

In July 2018, Roche Products Ireland Ltd made a submission on pertuzumab (Perjeta®) (in combination with trastuzumab and chemotherapy) for the adjuvant treatment of adult patients with HER2-positive breast cancer at high risk of recurrence (defined here as patients with node-positive or hormone receptor-negative disease). The comparator is trastuzumab (in combination with chemotherapy). Final data, required by the NCPE, was received on 18th January 2019.

1. Comparative effectiveness of pertuzumab (in combination with trastuzumab and chemotherapy)

Evidence was derived from the on-going phase III, randomised, double-blind, placebo-controlled APHINTY study. APHINITY evaluates pertuzumab (in combination with trastuzumab and chemotherapy) versus trastuzumab (in combination with chemotherapy) in patients with HER2-positive early breast cancer with either node-positive or node-negative disease. The trial protocol was amended after about 75% of the population had been randomised; patients with node-negative disease were no longer eligible. This amendment resulted in the intention-to treat population being enriched with patients with node-positive disease. Thus the intention-to-treat population may not be representative of all patients with HER2-positive early breast cancer.

The primary endpoint was the composite Invasive Disease-Free Survival (IDFS) in the intention-to-treat population. The usefulness of IDFS event-free rates as a surrogate for longer-term outcomes is unclear. The Kaplan Meir IDFS curves overlap up to 2 years. In the intention-to-treat population, the 3 year IDFS event-free rates were 94.1% and 93.2% in the pertuzumab (in combination with trastuzumab and chemotherapy) and trastuzumab (in combination with chemotherapy) arms respectively; hazard ratio (HR) = 0.81, 95% CI 0.66 - 1.00. The 4-year rates were 92.3% and 90.6% respectively; HR = 0.82, 95% CI 0.67 - 1.00. The results observed in the intention-to-treat population could appear to be driven by the node-positive subgroup. The overall survival data are immature; at the time of the primary analysis there was no apparent difference between the treatment arms.

Subgroup analyses were performed for IDFS event-free rates. Subgroup analyses were not performed for all known prognostic factors (including tumour grade and ethnicity). The analyses are described as exploratory only; they were not powered to detect statistical significance. There are concerns regarding the potential lack of adjustment for multiple hypotheses being tested which may suggest there could be false positive results in this analysis. It is not clear, from the data available to the Review Group, how many patients had at least one risk factor. On review of the outcomes of the subgroup analyses, it is not clear why pertuzumab would only be considered in patients with node-positive or hormone receptor-negative disease. In particular, no significance was detected in patients with hormone receptor-negative disease, whilst significance was seen in a number of other subgroups.

The original submission included two distinct base cases; one which pertains to patients with node-positive disease and one which pertains to patients with hormone receptor-negative disease. Given the issues highlighted above, the Review Group requested that the two base case analyses should pertain to the pre-protocol amendment population from APHINITY and to the intention-to-treat population from APHINITY. The applicant declined to make these changes. Model functionality allowed the NCPE to investigate cost effectiveness in the APHINITY intention-to-treat population.

2. Safety of pertuzumab (in combination with trastuzumab and chemotherapy)

In the APHINITY study, patients who received at least one dose of study treatment were included in safety analyses. At least one adverse event was experienced in 99.9% and 99.5% of patients in the pertuzumab (in combination with trastuzumab and chemotherapy) and trastuzumab (in combination with chemotherapy) arms respectively. Grade ≥ 3 adverse events occurred in 64.2% and 57.3% of patients in the respective arms. The most common were neutropenia (16.3% vs 15.7%), febrile neutropenia (12.1% vs 11.1%), decreased neutrophil count (9.6% vs 9.6%), diarrhoea (9.8% vs 3.7%) and anaemia (6.9% vs 4.7%). Primary cardiac events (symptomatic cardiac dysfunction) occurred in 0.7% and 0.3% of patients in the respective arms. New York Heart Association (NYHA) III/IV Heart Failure with a drop in LVEF ≥10 ejection fraction points from baseline and to below 50% occurred in 0.6% and 0.2% of the respective arms. Cardiac death (definite or probable) occurred in 2 patients

in each arm. Secondary cardiac events (asymptomatic or mildly symptomatic (NYHA Class II) significant LVEF drop of at least 10 ejection fraction points below baseline and to below 50%) occurred in 2.7% and 2.8% of the respective arms. A fatal adverse event occurred in 0.8% of patients in both arms.

3. Cost effectiveness of pertuzumab (in combination with trastuzumab and chemotherapy)

Cost effectiveness of pertuzumab (in combination with trastuzumab and chemotherapy) versus trastuzumab (in combination with chemotherapy) was evaluated using a lifetime horizon model with six health states.

All patients start in the 'IDFS' health state. Modelling of IDFS events uses parametric extrapolation of the APHINITY data along with data from longer follow-up trials (BCIRG 006 and HERA) and a number of other assumptions. Rates of metastatic and non-metastatic recurrences were derived from APHINITY. The pooled proportion of metastatic and non-metastatic recurrences were applied to both arms in the model. It is not clear why the data was pooled or how this pooling would affect the results. The model assumes that all patients in 'Non-Metastatic Recurrence' would undergo one year of additional adjuvant therapy. The Review Group consider the assumption that zero patients would progress to metastatic breast cancer within 12 months to be highly uncertain. Following the adjuvant therapy, patients who are still alive automatically transition to the 'Remission' state. When in remission, patients can either die or experience an additional recurrence. The analysis assumes that any additional recurrence would always be metastatic; no evidence was provided to support this assumption. In the 'First-Line Metastatic Breast Cancer' state, the risk of further disease progression and death depends on the treatment that patients are likely to receive here. In the 'Subsequent-Lines Metastatic Breast Cancer' state, the risk of death depends on the treatment that patients are likely to receive here. The 'Death' state is the absorbing state. The risk of death is adjusted to the background female mortality for each health state.

In the base case, APHINITY EQ-5D -3L data was used to derive utilities for the early breast cancer states. For the original analysis, responses from both arms were pooled. The Review

Group consider that any differences between arms should be considered. The applicant changed the base case to reflect un-pooled responses. The analysis assumes that any disutility resulting from adverse events are already reflected in the APHINITY EQ-5D-3L data. This approach will underestimate the associated disutility, particularly given the infrequency of the collection of data in APHINITY. In APHNITY, the EQ-5D was not administered to patients who had progressed. Utilities for the metastatic breast cancer states were derived from Lloyd *et al*. The Review Group have reviewed this publication. It is not immediately clear which parameter estimates from Lloyd *et al* were used to estimate the utilities used in this analysis. The Review Group requested clarification; adequate clarification was not provided.

During the Review Group evaluation, the applicant provided results of an updated elicitation which identified the standard of care chemotherapy regimens used in Ireland. Usage identified was 41% AC-T (doxorubicin, cyclophosphamide and taxane), 35% TC (taxane and carboplatin) and 24% taxane monotherapy. The applicant updated the model with this data, however only costs (and not efficacy data) were updated. The Review Group note that these regimens are not reflective of all regimens in APHINITY (from where the efficacy data input in the model is derived).

The model included drug acquisition costs, drug administration, monitoring costs, health state costs, supportive care costs, and costs associated with adverse events. Drug dosages, treatment durations, monitoring and pre-medication requirements were derived from the respective licenses and National Cancer Control Programme treatment protocols. Health state costs were informed by international guidelines, market research, published literature, National Cancer Control Programme treatment protocols and a number of assumptions. The applicant included only 'treatment-related Grade ≥ 3 adverse events' which occur in ≥ 2% of patients. This approach will underestimate the impact of adverse events on costs.

A discount rate of 5% was used for both costs and outcomes in the base case analysis.

In the applicant's analysis, the deterministic incremental cost-effectiveness ratios (ICERs) are €58,285/QALY (€38,381/ 0.66) in the population with node-positive disease and

€93,951/QALY (€43,274/ 0.46) in the population with hormone receptor-negative disease. Model functionality allowed the Review Group to investigate cost effectiveness in the APHINITY intention-to-treat population. All other applicant assumptions remain unchanged. The ICER is €104,983/QALY (€42,933/ 0.41). This intention-to-treat population (enriched with patients with node-positive disease) may not be representative of all patients with HER2-positive early breast cancer. Thus, this ICER may be an underestimate of the ICER in such a population. The Review Group notes the relatively large incremental QALY gains seen in all three evaluations. This is despite the small sustained difference in efficacy seen in the APHINITY data.

The Review Group implemented their preferred assumptions in the model. We assume that from 36 months onwards, the proportion of patients being cured starts at 0% (the original submission assumed that this occurred from 48 months onwards). We assume that waning of the treatment effect begins at 4 years (the original submission assumed that this occurred at 7 years). The resultant ICERs are €75,400/QALY (€40,734/ 0.54) in the population with node-positive disease and €107,560/QALY (€49,736/ 0.41) in the population with hormone receptor-negative disease. For the intention-to-treat analysis, we implemented the most conservative extrapolation of the IDFS curve (due to a lack of available informative data on the best fit parametric curve). The resultant ICER is €174,149/QALY (€46,192 / 0.27). Similar to above, the ICER in the intention-to-treat population may be an underestimate.

Deterministic sensitivity analyses indicate that the time horizon has the largest impact on the ICER in all of the above evaluations. The deterministic and the respective probabilistic ICERs are comparable in all instances. The probability of cost effectiveness is 0% at both the €20,000/QALY and €45,000/QALY thresholds in all of the evaluations.

4. Budget impact of pertuzumab (in combination with trastuzumab and chemotherapy)

Pertuzumab is supplied in a single 420mg/14ml vial (as concentrate for infusion). The price to wholesaler for a single 420mg vial is €2,761.65. The recommended initial loading dose is 840mg (intravenous infusion over 60-minutes) followed every three weeks by maintenance

of 420mg (intravenous infusion over 30-60 minutes). In the adjuvant setting, it is administered every three weeks for a total of one year (18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first). The cost of pertuzumab is €61,653.86 per patient per year inclusive of 23% VAT and rebate.

The applicant's budget impact analysis considers patients with HER2-positive early breast cancer who are at high risk of recurrence (specifically defined here as patients with node-positive disease or hormone receptor-negative disease). Under the applicant's assumptions, there are approximately 231 patients eligible for adjuvant treatment with pertuzumab in Year 1. The applicant assumes that the uptake rate in Year 1 will be 30% and will increase to 60% in Year 5. Under these assumptions, it is estimated that 69 patients will be treated in Year 1 increasing to 149 in Year 5. The Review Group queried the seemingly low uptake rates. No changes were made. The budget impact assumes 100% dose intensity; it assumes that all patients will receive 18 cycles of treatment. The budget impact does not take account of mortality.

Dissimilar to the updated cost-effectiveness analysis, the budget impact model assumes that 75% of patients will receive AC-T (doxorubicin, cyclophosphamide and taxane) and 25% will receive TC (taxane and carboplatin). This is not reflective of all chemotherapy regimens used in Ireland. A weighted mean cost for chemotherapy is applied to both the treatment and comparator arms.

Under the applicant's assumptions, the budget impact of treatment with pertuzumab (in combination with trastuzumab and chemotherapy) is about €6.67 million in Year 1, increasing to about €14.40 million in Year 5. The 5-year cumulative gross impact is about €52.36 million. The Review Group consider that this budget impact is potentially underestimated due to the assumption of a relatively low uptake rate. Of note, this budget impact assumes that pertuzumab will only be used in patients with node-positive or hormone receptor-negative disease.

Given that pertuzumab will be added to currently used regimens (i.e. trastuzumab in combination with chemotherapy), the net budget impact is equivalent to the gross budget impact.

5. Patient submissions.

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

6. Conclusion

Following NCPE assessment of the company submission, the NCPE recommends that pertuzumab (in combination with trastuzumab and chemotherapy) for the adjuvant treatment of adult patients with HER2-positive breast cancer at high risk of recurrence (defined here as patients with node-positive or hormone receptor-negative disease), 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.