Cost-effectiveness of trastuzumab emtansine (Kadcyla®) as a single agent, for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of trastuzumab emtansine (Kadcyla®). Following assessment of the Applicant's submission, the NCPE recommends that trastuzumab emtansine (Kadcyla®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

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 trastuzumab emtansine (Kadcyla®). 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.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

National Centre for Pharmacoeconomics **March 2021**

Summary

In June 2020, Roche Products (Ireland) Ltd submitted a dossier examining the clinical effectiveness, safety and economic evidence for trastuzumab emtansine (Kadcyla®) as a single agent, for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy. Final data submitted by the Applicant was received in November 2020. Reimbursement is being sought under the Oncology Drugs Management Scheme.

Trastuzumab emtansine is an antibody-drug conjugate which covalently links the HER2-targeted monoclonal antibody, trastuzumab, to the microtubule inhibitor DM1. Trastuzumab emtansine is administered via intravenous infusion at a dose of 3.6 mg/kg bodyweight once every 21-day cycle. Treatment should continue for 14 cycles or until there is disease recurrence or unacceptable toxicity.

In Ireland, approximately 15% of all breast cancers are characterised by overexpression of HER2 (known as HER2-positive breast cancer). Compared to HER2-negative disease, this subtype is associated with an aggressive clinical phenotype and increased mortality. When diagnosed at an early stage, treatment intent is curative. For patients who receive neoadjuvant treatment with HER2-targeted therapy and chemotherapy, the finding of residual invasive disease at surgery is associated with a poorer prognosis, as compared to those who do not have residual disease. At present, patients with early, HER2-positive breast cancer who are treated in the neoadjuvant setting (with HER2-targeted therapy and chemotherapy) receive one year of adjuvant trastuzumab therapy, irrespective of the presence of residual disease at the time of surgery. Trastuzumab was considered as the primary comparator in the submission. Pertuzumab is licensed for use in combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with early, HER2-positive breast cancer at high risk of recurrence. Reimbursement is not currently agreed for this treatment; however, pertuzumab in combination with trastuzumab and chemotherapy was considered as a comparator in a scenario analysis.

1. Comparative effectiveness of trastuzumab emtansine

Direct comparative clinical evidence for trastuzumab emtansine in the adjuvant setting was sourced from the KATHERINE trial. This is an ongoing, phase III, randomised, open-label trial evaluating the safety and efficacy of trastuzumab emtansine versus trastuzumab in patients with HER2-positive breast cancer, with residual tumour in the breast or axillary lymph nodes following neoadjuvant therapy. A total of 1,486 patients were randomised on a 1:1 basis to receive either trastuzumab emtansine (3.6 mg/kg) or trastuzumab (6 mg/kg), both of which were administered intravenously once every 21-day cycle for 14 cycles until disease recurrence or unmanageable toxicity. The primary endpoint was invasive disease-free survival (iDFS); secondary endpoints included disease-free survival (DFS), overall survival (OS) and patient-reported outcomes including the EuroQol-5D (EQ-5D) instrument.

The median duration of follow-up at the clinical cut-off date (July 2018) was 41.0 months. For the primary efficacy endpoint, 91 patients (12.2%) in the trastuzumab emtansine arm had experienced an iDFS event, as compared to 165 patients (22.2%) in the trastuzumab arm (hazard ratio [HR] 0.50; 95% confidence interval [CI]: 0.39 to 0.64; p<0.0001). OS data are immature: 42 patients (5.7%) in the trastuzumab emtansine arm had died, as compared to 56 patients (7.5%) in the trastuzumab arm (HR 0.70; 95% CI: 0.47to 1.05; p=0.0848).

Based on the available data, a major source of uncertainty is whether or not trastuzumab emtansine will result in a long-term reduction in the risk of breast cancer recurrence as compared to trastuzumab, or if the iDFS gains observed to date instead reflect a delay in the occurrence of iDFS events (and these have not yet been observed). Additional analyses whereby data is available for the majority of the study of the population up to five years will likely reduce this uncertainty after this point. Furthermore, OS data are immature. It is unclear if the early improvements in iDFS observed to date in KATHERINE will translate to improvements in survival.

To inform a scenario analysis, the Applicant conducted an indirect treatment comparison of trastuzumab emtansine and pertuzumab in combination with trastuzumab and chemotherapy by combining evidence from the KATHERINE and APHINITY studies. The approach used was not methodologically justified due to considerable differences in the

study populations and pre-randomisation treatment pathways, and was considered by the Review Group to be of limited value for decision making.

2. Safety of trastuzumab emtansine

The type of adverse events (AEs) observed in the KATHERINE trial did not differ from the known safety profile of trastuzumab emtansine. These include hepatotoxicity, thrombocytopenia, peripheral neuropathy, haemorrhage, infusion-related reactions and pulmonary toxicity. However, the frequency and severity of trastuzumab emtansine-specific AEs appears to be increased in the adjuvant setting as compared to the metastatic setting. This may be partly explained by the longer duration of exposure in the clinical trial (KATHERINE: median cycles = 14; EMILIA [metastatic breast cancer]: median cycles = 9). In KATHERINE, a substantially higher proportion of patients discontinued study treatment due to AEs in the trastuzumab emtansine arm than the trastuzumab arm (18% vs. 2%, respectively). Of all patients randomised to trastuzumab emtansine, 9.6% discontinued study treatment and were switched to trastuzumab.

3. Cost effectiveness of trastuzumab emtansine

Methods

The Applicant submitted a probabilistic state transition (semi-) Markov model consisting of six states: iDFS, non-metastatic recurrence, remission, first-line metastatic breast cancer, subsequent-lines metastatic breast cancer and death. Cycle length was one month and a half-cycle correction was applied. A 51-year time horizon was used, with a starting age of 49 years.

Treatment effectiveness was modelled primarily via the length of time spent in the iDFS health state, which was estimated by extrapolating the KATHERINE iDFS data, adjusted to account for the decreased risk of recurrence after years three to five. Once patients experience disease recurrence, no further difference in the probabilities of recurrence, progression or death between treatment arms was assumed. As such, the increased length of time spent in the iDFS state by patients treated with trastuzumab emtansine leads indirectly to greater overall survival by preventing and/or delaying metastatic disease, and to improved quality of life. The Review Group expressed concern with regards to the

immaturity of the KATHERINE iDFS data and the reliance on extrapolation, which is the greatest area of uncertainty in the model. The Review Group also remain concerned about the immaturity of the KATHERINE OS data

Utilities were modelled through health state-specific utility values, which were independent of treatment received. Disutilities were not incorporated to reflect utility loss as a result of treatment-related AEs, which the Review Group identified as a limitation of the modelling approach used. The model was not sensitive to a scenario examining the application of disutilities. Costs applied in the model included costs related to the following: drug acquisition costs, drug administration costs, treatment monitoring costs, costs associated with AEs, supportive care costs and end-of-life care costs. For the iDFS health state, treatment specific costs were applied for drug acquisition costs, administration, treatment monitoring and AE-related costs. All other costs applied in the model were independent of treatment arm. The Review Group expressed concern that the treatment costs associated with post-progression health states did not account for time off treatment, and therefore over-estimated costs in these health states. This was addressed by the Review Group in the NCPE-adjusted base case.

Results

The results of the Applicant's base case analysis are presented in Table 1. The Review Group identified a number of limitations to the Applicant's base case which were addressed in the NCPE adjusted base case (Table 2). Key changes included:

- Shortening the assumed duration of treatment effect for trastuzumab emtansine, by adjusting the timing of effect ranging from 7-10 years to 4-7 years
- Removing the assumption that all recurrences during the first 18 months would be exclusively metastatic in nature
- Reducing the treatment costs in the metastatic setting to account for time off treatment
- The calculation of drug acquisition costs for trastuzumab was changed to account for (partial) vial sharing, different market share assumptions for trastuzumab products, and discounts for intravenous trastuzumab biosimilar products.

Table 1 Results of deterministic incremental cost-effectiveness analysis – Applicant's corrected base case^

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)*
Trastuzumab emtansine	114,063	12.63	4,787	1.49	3,222
Trastuzumab	109,276	11.15			

ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.
^ Applicants results with minor coding errors corrected.

Table 2 Results of deterministic incremental cost-effectiveness analysis – NCPE-adjusted base case

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)*
Trastuzumab emtansine	117,592	12.26	16,043	1.09	14,774
Trastuzumab	101,550	11.17			

ICER: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
*A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

The Review Group highlight that there is significant uncertainty with regard to the cost-effectiveness of trastuzumab emtansine:

- The immaturity of the iDFS data and the reliance of the model on extrapolation to demonstrate benefit is a major source of uncertainty. For context, almost 96% of the incremental QALYs are accrued after year four, whereas the median follow-up in the KATHRINE trial was approximately 41 months. If the early iDFS improvement observed to date in the KATHERINE trial reflects recurrences being delayed rather than prevented entirely, this gain in QALYs will be considerably reduced. A number of scenarios were presented by the Review Group to examine the impact of this uncertainty on the cost-effectiveness analysis. The ICER varied between €25,051 per QALY and €138,608 per QALY, depending on the proportion of recurrences delayed rather than prevented by trastuzumab emtansine.
- There is uncertainty around the survival benefit predicted by the model, which suggests trastuzumab emtansine is associated with improved OS. The OS data available from the KATHERINE trial is immature, and as such cannot be used to validate the model outputs.

Sensitivity analysis

Under the NCPE-adjusted base case, the probability of cost-effectiveness at willingness-to-pay thresholds of €20,000 per QALY and €45,000 per QALY were 64% and 95%, respectively.

4. Budget impact of trastuzumab emtansine

The price to wholesaler of trastuzumab emtansine is €1,551.17 per 100 mg vial and €2,481.88 per 160 mg vial. Drug costs were calculated based on the combinations of vials required per bodyweight band, and weighted by the distribution of bodyweight in the KATHERINE trial population. Assuming no discontinuations or dose reductions, the expected cost per treatment course per patient is €71,196.97, including VAT (23%). The Applicant proposed that the number of patients receiving treatment will increase from 135 in year 1 to 206 in year 5. The Review Group expressed concern that this underestimated the proportion of patients with early, HER2-positive breast cancer expected to receive treatment in the neoadjuvant setting (and therefore potentially be eligible for treatment with trastuzumab emtansine). The Review Group estimated that the number of patients receiving treatment will increase from 196 in year 1 to 228 in year 5. This reflects clinical opinion obtained by the Review Group, allowing for increased use of neoadjuvant therapy over time. Under these assumptions, the NCPE-adjusted 5-year gross drug budget impact is expected to be €56 million. Following displacement of trastuzumab, the NCPE-adjusted 5-year cumulative net drug budget impact was €38.4 million. The Applicant did not include any additional costs or cost offsets as part of the submission.

5. Patient submission

No patient submissions were received for this assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that trastuzumab emtansine (Kadcyla®) be considered for reimbursement if 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.