Cost Effectiveness of trastuzumab emtansine (Kadcyla®), as a single agent for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the use of trastuzumab emtansine for this indication. The NCPE do not recommend reimbursement of trastuzumab emtansine at the submitted price.

The HSE has asked the NCPE to evaluate the manufacturer's (Roche Products (Ireland) Ltd) economic dossier on the cost effectiveness of trastuzumab emtansine. 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 that 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 that may be relevant for the decision; the final decision on reimbursement is made by the HSE. As this is an oncology drug, 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 **June 2014**

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Trastuzumab-emtansine is an antibody drug conjugate incorporating the human epidermal growth factor receptor 2 (HER2)-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1.

In February 2014, Roche Products (Ireland) Ltd submitted an economic evaluation to the National Centre for Pharmacoeconomics (NCPE) on the cost effectiveness of trastuzumab emtansine for this indication. The evaluation uses an Area under the Curve model with three health states: 'Progression Free Survival', 'Progression' and 'Death'. The model has a 15 year time horizon; costs and consequences are discounted at 5%. The Company identified the following comparators, in order of most commonly used (via market research):

- Trastuzumab + chemotherapy (assumed to be docetaxel)
- Lapatinib + capecitabine
- Trastuzumab + lapatinib
- Trastuzumab + capecitabine
- Capecitabine monotherapy

The clinical evidence for trastuzumab emtansine originates from the EMILIA randomised controlled trial which compares trastuzumab emtansine to lapatinib + capecitabine [1]. Exclusion criteria included prior treatment with lapatinib or capecitabine; there is no data available on the effectiveness of trastuzumab emtansine in patients who have received either drug.

For the economic model, extrapolation beyond the trial follow-up period was performed on the progression free survival and overall survival data by fitting the best fit parametric curves to the empirical Kaplan-Meier estimates. The model was developed using investigator assessed progression free survival; this data will be more

liable to bias than the independently assessed progression free survival data. This will introduce uncertainty into the economic evaluation.

The primary comparator is trastuzumab + chemotherapy. The Review Group has concerns that no direct or indirect evidence compares trastuzumab emtansine to this primary comparator. A network meta-analysis was conducted to assess the efficacy of trastuzumab emtansine against trastuzumab + capecitabine and capecitabine monotherapy. The progression free survival and overall survival curves for trastuzumab + capecitabine are assumed to be a proxy for trastuzumab + chemotherapy and trastuzumab + lapatinib. No clinical data has been presented to support this assumption.

Adverse event rates for input into the economic model were not derived from the network meta-analysis. Adverse events costs for all the indirect comparison arms were assumed to be the same as for the lapatinib + capecitabine arm of the EMILIA trial. Utility values were derived from the literature. Trastuzumab + capecitabine progression free survival utility values were assumed to be a proxy for the trastuzumab + chemotherapy and trastuzumab + lapatinib progression free survival utility values.

In this summary we report the results of the cost-effectiveness analyses of trastuzumab emtansine compared to the primary and secondary comparators. The deterministic incremental costs effectiveness ratios (ICERs) were €82,683/QALY (vs. trastuzumab + chemotherapy) and €149,838/QALY (vs. lapatinib + capecitabine). These basecase analyses assume an average patient weight of 70kg. However, there is some evidence to support an average weight of 73kg in a local cohort of female patients with breast cancer. The ICERs increase to €123,780/QALY (vs. trastuzumab + chemotherapy) and €224,620/QALY (vs. lapatinib + capecitabine) when this average weight is assumed.

Deterministic sensitivity analyses indicate that the ICERs are particularly sensitive to a number of other parameter changes: the utility value attached to the progression free survival Health States, the hazard ratio applied to the overall survival curves, the

parametric model chosen to extrapolate the empirical survival data and the time horizon of the economic model.

The probabilistic sensitivity analysis (PSA) (assumes an average patient weight of 70kg) indicates that the probability of trastuzumab emtansine being cost effective at €45,000/QALY is 1% vs. trastuzumab + chemotherapy and 0% vs. lapatinib + capecitabine. Probabilities versus the other comparators are also low. We note that the probabilistic ICERs (which take into account some decision uncertainty) are higher than the deterministic ICERs, €98,809/QALY (vs. trastuzumab + 'chemotherapy' and €162,938/QALY (vs. lapatinib + capecitabine). Since probabilistic ICERs take some decision uncertainty into account they are likely to be more realistic than the deterministic ICERs.

The Company estimate that the 5 year cumulative gross budget impact will be in the region of €19.74 million. The 5 year net budget impact is estimated to be about €11.54 million. This budget impact assumes that the total number of patients treated with trastuzumab emtansine will fall annually over the 5 year period. It also assumes an average patient weight of about 72kg. In reality the budget impact may be higher; it is sensitive to the assumption that the total number of patients will fall annually and to the assumed average patient weight.

The NCPE Review Group concludes that, at the current price, trastuzumab emtansine is not cost effective for this indication. The primary comparator (according to market research) is trastuzumab + chemotherapy. The main areas of concern are that the clinical and utility data were derived by assuming that trastuzumab + capecitabine is a proxy for trastuzumab + chemotherapy. For AE costs, lapatinib + capecitabine is assumed to be a proxy for trastuzumab + chemotherapy. Neither assumption is supported by clinical evidence. The NCPE Review Group believes that the ICER (vs. trastuzumab + chemotherapy) is associated with a high degree of uncertainty.

Of note, it has been highlighted, by both the U.S. Food and Drug Administration and the European Medicines Agency, that there exists a risk of potential medication errors resulting from name similarity between trastuzumab and trastuzumab emtansine.

There are concerns that this could lead to dosing errors and potential harm to patients [2, 3].

References

1. Verma S, Miles D, Gianni L, Krop I, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. for the EMILIA Study Group. N Engl J Med 2012;367(19):1783-1791.
2. Kadcyla (ado-trastuzumab emtansine): Drug Safety Communication - Potential Medication Errors Resulting from Name Confusion. U.S. Food and Drug Administration (FDA) Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm350817.htm [Accessed 18 June 2014].
3. European Medicines Agency.Assessment Report. Kadcyla (Trastuzumab emtansine). Procedure No. EMEA/H/C/002389/0000 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002389/WC500158595.pdf [18th June 2014].