Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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trastuzumab emtansine, 100mg and 160mg, powder for concentrate for solution for infusion (Kadcyla®) SMC No. (990/14)

Roche Products Ltd.

10 March 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a resubmission assessed under the orphan equivalent and end of life process

trastuzumab emtansine (Kadcyla®) is accepted for use within NHS Scotland.

Indication under review: as a single agent, for the treatment of adult patients with human epidermal growth factor type 2 (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 six months of completing adjuvant therapy.

In a randomised phase III open-label study, trastuzumab emtansine (Kadcyla®) conferred a significant survival benefit compared with an active comparator.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of trastuzumab emtansine (Kadcyla®). This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 10 April 2017

Indication

As a single agent, is indicated 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 six months of completing adjuvant therapy.

Dosing Information

3.6mg/kg bodyweight administered as an intravenous infusion every three weeks (21-day cycle). Patients should be treated until disease progression or unacceptable toxicity.

Patients treated with trastuzumab emtansine should have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) or a ratio of ≥2.0 by in situ hybridization (ISH) assessed by a CE-marked In Vitro Diagnostic (IVD) medical device. If a CE-marked IVD is not available, the HER2-status should be assessed by an alternative validated test.

Trastuzumab emtansine (Kadcyla®) should only be prescribed by a physician and administered under the supervision of a healthcare professional who is experienced in the treatment of cancer patients.

Product availability date

10 February 2014. Trastuzumab emtansine meets SMC end of life and orphan-equivalent criteria.

Summary of evidence on comparative efficacy

Trastuzumab emtansine (Kadcyla®) is an antibody-drug conjugate. It contains the humanised anti-HER2 immunoglobulin, trastuzumab, covalently linked to the microtubule inhibitor DM1 (a maytansine derivative) via a stable thioether linker. DM1 is too toxic to be administered alone but the linker limits systemic release of DM1, increasing targeted delivery to HER2-positive cancer cells and decreasing systemic adverse effects. Trastuzumab emtansine (Kadcyla®) has the mechanisms of action of both trastuzumab and DM1.[1]

Evidence to support the marketing authorisation for trastuzumab emtansine (Kadcyla®) comes from the pivotal EMILIA study,[2,4] a randomised, open-label, international study comparing the efficacy of trastuzumab emtansine (Kadcyla®) with lapatinib plus capecitabine in patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer that had previously been treated with trastuzumab and a taxane. Patients were required to have HER2-positive and measurable disease with disease progression during or after the most recent treatment for locally advanced or metastatic disease, or within six months of treatment for early stage disease. They also had good cardiac function and a performance status of 0 or 1. Patients were randomly assigned in a 1:1 ratio (with stratification according to world region, number of prior chemotherapy regimens and disease involvement) to receive trastuzumab emtansine (Kadcyla®) 3.6mg/kg of body weight intravenously every 21 days (n=495) or lapatinib 1,250mg orally daily continuously

plus capecitabine 1,000mg/m^2 of body-surface area orally every 12 hours for 14 days of a 21-day cycle (n=496). Treatment continued until disease progression or unmanageable toxicity.

The co-primary outcomes assessed in the intention to treat population were progression-free survival (PFS) as assessed by independent review and overall survival (OS). At the first data cutoff (median duration of follow-up approximately 13 months), median PFS was 9.6 months in the trastuzumab emtansine group and 6.4 months in the lapatinib plus capecitabine group; hazard ratio (HR) 0.65 (95% confidence interval [CI] 0.55 to 0.77, p<0.001). At the second interim analysis of OS (after 331 deaths and a median duration of follow-up of 19 months), trastuzumab emtansine (Kadcyla®) significantly increased median OS compared with lapatinib plus capecitabine; 30.9 months versus 25.1 months, HR 0.68 (95% CI 0.55 to 0.85, p<0.001). This was considered the confirmatory OS analysis and since results crossed the pre-specified stopping boundary, patients were then allowed to cross over from lapatinib plus capecitabine to trastuzumab emtansine. At the final OS descriptive analysis, after a median follow-up of 47.8 months in the trastuzumab emtansine group and 41.9 months in the lapatinib plus capecitabine group), median OS was 29.9 months and 25.9 months respectively; HR 0.75 (95% CI: 0.64 to 0.88), p=0.0003. At this analysis, 27% of lapatinib plus capecitabine patients had crossed over to trastuzumab emtansine and sensitivity analysis, in which crossover patients were censored, found median OS of 29.9 months and 24.6 months respectively; HR 0.69 (95% CI: 0.59 to 0.82).[1,7] Secondary outcomes are included in Table 1.

Table 1: Secondary outcomes

	Trastuzumab emtansine (Kadcyla®)	Lapatinib plus capecitabine	Statistical significance
Investigator-assessed PFS	9.4 months	5.8 months	HR 0.66 (95% CI: 0.56 to 0.77) p<0.001
Objective-response rate	44% (95% CI: 39% to 49%)	31% (95% CI: 26% to 36%)	p<0.001
Median duration of response	13 months (95% CI: 8.4 to 21)	6.5 months (95% CI: 5.5 to 7.2)	N/A

PFS=progression-free survival; HR=hazard ratio; N/A=not available

A consistent treatment benefit for PFS and OS associated with trastuzumab emtansine (Kadcyla®) was found in most of the pre-specified subgroups, supporting the overall results. However, results were less favourable for trastuzumab emtansine (Kadcyla®) compared with lapatinib plus capecitabine in older patients, patients with non-measurable disease at baseline and patients with non-visceral disease.[2,4]

Quality of life was assessed using the Trial Outcome Index of the patient-reported Functional Assessment of Cancer Therapy-Breast (FACT-B TOI). Scores range from 0 to 92 with higher scores indicating a better quality of life. Median time to a decrease of ≥5 points (minimally important difference) in the FACT-B TOI score was delayed in the trastuzumab emtansine (Kadcyla®) group compared with the lapatinib plus capecitabine group: 7.1 months versus 4.6 months, HR 0.8 (95% CI 0.67 to 0.95, p=0.012).[4]

The TH3RESA study[3] (an open-label, phase III study) was conducted in patients with progressive disease who had previously received two or more HER2-directed therapies for locally advanced or metastatic breast cancer, including trastuzumab and lapatinib in the metastatic setting, and a

taxane in any setting. Patients were randomised in a 2:1 ratio to receive trastuzumab emtansine (Kadcyla®) 3.6mg/kg intravenously every 21 days or treatment of physician's choice (TPC). The co-primary endpoints were PFS (assessed by the investigator) and OS. At a data cut-off in February 2013, 602 patients had been randomised, 404 to trastuzumab emtansine (Kadcyla®) and 198 to TPC. Most patients (68%) allocated to TPC received chemotherapy plus trastuzumab. After a median follow-up of 7.2 months in the trastuzumab emtansine (Kadcyla®) group and 6.5 months in the TPC group, PFS was significantly improved in the trastuzumab emtansine (Kadcyla®) group: 6.2 months versus 3.3 months, HR 0.53 (95% CI: 0.42 to 0.66, p<0.0001). The PFS benefit associated with trastuzumab emtansine (Kadcyla®) was consistent across the various subgroups. Interim analysis of OS showed a trend favouring trastuzumab emtansine (Kadcyla®) (HR 0.55 [95% CI: 0.37 to 0.83]) but the results did not cross the predefined stopping boundary. At a further analysis (February 2015 cut-off date), after a median follow-up of 30.9 months, median OS was 22.7 months with trastuzumab emtansine and 15.8 months with TPC (HR 0.68 [95% CI: 0.54 to 0.85]). At this point, 47% of patients had crossed-over to trastuzumab emtansine; the crossover-adjusted HR for OS was 0.58.[8]

Summary of evidence on comparative safety

Almost all patients reported an adverse event during the EMILIA study[2]: 96% of patients receiving trastuzumab emtansine (Kadcyla®) and 98% of patients receiving lapatinib plus capecitabine. Fewer adverse events of at least grade 3 severity were reported in the trastuzumab emtansine (Kadcyla®) group than in the lapatinib plus capecitabine group (41% versus 57%) and fewer (5.9%) patients discontinued trastuzumab emtansine (Kadcyla®) due to adverse events, compared with 7.6% of patients who discontinued lapatinib and 9.4% who discontinued capecitabine.

In the EMILIA study, serious adverse events were reported by 16% of trastuzumab emtansine (Kadcyla®) and 18% of lapatinib plus capecitabine treated patients. The most commonly reported grade 3 or 4 adverse events in the trastuzumab emtansine (Kadcyla®) group were thrombocytopenia, elevated aspartate aminotransferase (AST) and elevated alanine aminotransferase (ALT). Grade 3 or 4 thrombocytopenia occurred in 13% of trastuzumab emtansine (Kadcyla®) treated patients compared with 0.2% of lapatinib plus capecitabine treated patients. Grade 3 or 4 elevated AST and ALT occurred in 4.3% and 2.9% of trastuzumab emtansine (Kadcyla®) treated patients compared with 0.8% and 1.4% of lapatinib plus capecitabine treated patients, respectively.

The most commonly reported grade 3 or 4 adverse events in the lapatinib plus capecitabine group were diarrhoea (21% versus 1.6% in the trastuzumab emtansine [Kadcyla®] group) and palmar-plantar erythrodysaesthesia (16% versus nil in the trastuzumab emtansine [Kadcyla®] group).

The overall incidence of bleeding was higher in the trastuzumab emtansine (Kadcyla®) group (30% versus 16%) but the rate of grade 3 or 4 bleeding events was low (1.4% versus 0.8%).[1]

Summary of clinical effectiveness issues

Breast cancer is the most common cancer diagnosed in women in Scotland. Metastatic breast cancer is incurable and SMC clinical experts suggest that there is an unmet need for effective therapies for patients with HER2-positive metastatic breast cancer who have received previous treatment with trastuzumab and a taxane. Trastuzumab emtansine (Kadcyla®) meets SMC end of life criteria and orphan drug criteria.

The EMILIA study demonstrated a statistically significant and clinically relevant improvement in both PFS and OS in patients with HER2-positive metastatic breast cancer treated with trastuzumab emtansine (Kadcyla®) compared with lapatinib plus capecitabine. Quality of life was maintained for longer in the trastuzumab emtansine (Kadcyla®) group compared with the lapatinib plus capecitabine group.[2]

The EMILIA study was open-label; this is standard practice in oncology, particularly when comparing an intravenous treatment with an oral treatment. The PFS endpoint was therefore assessed by independent review. However, the oncology reviewer was inadvertently given information on toxicities and this may have introduced bias in the adjudication of PFS.[2] Reporting of adverse events and patient reported outcomes may have been biased by the open label design of the study. The OS benefit of trastuzumab emtansine (Kadcyla®) treatment was demonstrated at the second interim analysis, subsequently defined as confirmatory. Although 27% of lapatinib plus capecitabine patients crossed over to trastuzumab emtansine by the time of the final OS analysis, sensitivity analysis censoring for crossover, found similar results.[1,7] In the EMILIA study, 62% and 37% of patients had a performance status of 0 and 1 respectively.[2]

Lapatinib plus capecitabine is not recommended by SMC for use in patients with metastatic breast cancer. Patients with HER2-positive metastatic breast cancer who have been previously treated with a taxane and trastuzumab may be treated with oral capecitabine or oral or intravenous vinorelbine.[5] In addition, SMC clinical experts suggest that there may be off-label use of trastuzumab in this setting. Clinical experts consulted by SMC considered that trastuzumab emtansine (Kadcyla®) is a therapeutic advancement over current therapies due to improved efficacy and reduced toxicity.

Since there are no comparative data with capecitabine monotherapy or capecitabine plus trastuzumab, the submitting company presented results of a mixed treatment comparison (MTC) using Bayesian methodology and a random-effects model. Data from six studies were included in the base case analysis to estimate the relative efficacy of trastuzumab emtansine (Kadcyla®) versus capecitabine or capecitabine plus trastuzumab in terms of PFS and OS. The final OS results from EMILIA, using the Rank Preserving Structural Failure Time (RPSFT) method to adjust for crossover, were included in the MTC. The results of point estimates of hazard ratios of the MTC suggest that trastuzumab emtansine (Kadcyla®) is more effective than capecitabine monotherapy and capecitabine plus trastuzumab in terms of PFS and OS. However, the credible intervals included 1 for all comparisons except PFS versus capecitabine monotherapy thereby indicating uncertainty. Results of sensitivity analyses, which excluded two of the six studies considered to be less comparable, also numerically favoured trastuzumab emtansine (Kadcyla®). The main limitations of the MTC were a lack of assessment of heterogeneity and no consideration of the relative safety outcomes of trastuzumab emtansine (Kadcyla®) and comparators. In addition, no results of probability of being best or rankings were reported. It was not possible to include vinorelbine in the MTC network and the submitting company assumed that the efficacy of

vinorelbine and capecitabine would be similar. This assumption was supported by SMC clinical experts.

Regular monitoring is required for the adverse effects of trastuzumab emtansine (Kadcyla®), including platelet count, liver and cardiac function and for signs/symptoms of neurotoxicity.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of trastuzumab emtansine, as an end of life and orphan-equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were

- Metastatic breast cancer is an aggressive sub-type which results in visceral/CNS metastases and severe symptoms. The outlook is very poor in this patient group.
- This is an effective therapy delivering a step change in treatment, including unprecedented survival and quality of life benefits.
- This has become standard of care in many other countries and treatment in Scotland is lagging behind leading to inequities with a negative psychological impact on patients and their families/carers.
- The improved tolerability may allow an excellent quality of life and an opportunity to function normally which contrasts sharply with expectations of life with metastatic breast cancer.
- Clinical experience with this medicine has demonstrated that patients may be able to return to work, care for children, engage in social activities and maintain good relationships. This also has a positive impact on the patient's carer and family e.g. the patient's partner maintaining employment rather than having to provide full time care for the patient and/or their children.
- The PACE group was very strongly supportive of this medicine being made available in NHS Scotland.

Addition of Patient and Carer Involvement

We received a joint patient group submission from Breast Cancer Care and Breast Cancer Now, both are registered charities. Breast Cancer Care has received less than 5% pharmaceutical company funding in the past two years, including from the submitting company. Breast Cancer Now has received 0.62% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both charities participated in a meeting to update the PACE statement. The key points of their submissions have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing trastuzumab emtansine (Kadcyla®) with capecitabine in patients with HER2 positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane separately or in combination. Comparisons were also provided with vinorelbine and capecitabine plus trastuzumab. A partitioned survival model was used which included three health states: progression-free survival, progressed disease and dead. The time horizon of the analysis was lifetime, which equated to a maximum duration of 15 years.

The clinical data used in the model were based on the outcomes from the EMILIA study plus the results of the MTC. In order to adjust for crossover in the lapatinib plus capecitabine arm in the EMILIA study,[2] the RPSFT method was used. PFS and OS estimates were then extrapolated by fitting parametric functions to the adjusted study data. A range of functions was tested using goodness of fit statistics and visual inspection of the curve fits to the Kaplen-Meier (KM) data. The log normal and gamma distributions were the best fit for PFS, with the base case analysis using the gamma distribution fitted to the tail of the KM data. The log logistic was the best fit for OS, but the company argued the gamma distribution would be more appropriate based on the face validity of the estimates over the longer term. In order to estimate PFS and OS for the capecitabine arm of the model, the company adjusted the extrapolated data to estimate the relative efficacy of trastuzumab emtansine (Kadcyla®) versus capecitabine alone by applying the HRs from the MTC (PFS HR = 0.40 and OS HR = 0.58). For the comparison with vinorelbine, the PFS and OS estimates for capecitabine were assumed to be a reasonable proxy for the efficacy of vinorelbine on the assumption that these treatments are seen as interchangeable. For the comparison with capecitabine plus trastuzumab, the HRs applied were 0.66 for PFS and 0.69 for OS, based on the MTC.

The utility values were estimated using methods from a published UK study which used standard gamble to estimate quality of life at distinct stages of metastatic breast cancer in members of the public.[9] For PFS, the utility value was estimated separately for each arm of the model by adjusting the value for stable disease using the relative response rates. This resulted in a higher utility value for patients in PFS on trastuzumab emtansine (Kadcyla®) than those in PFS on capecitabine (0.807 vs 0.792). For the comparisons with vinorelbine and capecitabine plus trastuzumab, the PFS utility values were 0.792 and 0.800 respectively. The utility value for progressed disease was estimated to be 0.53. Disutilities were applied in the model for grade 3 or 4 adverse events affecting more than 3% of patients in either treatment arm and also considered to have an impact on quality of life according to clinical opinion. This resulted in utility decrements being applied for diarrhoea, fatigue and hand and foot syndrome.

The cost of the medicines, administration costs and pharmacy costs are included. No vial sharing was assumed thus all calculations of medicine costs include drug wastage. Adverse events costs are also included. Other resource use estimates were taken from acceptable published sources and were applied in the model according to each health state. The costs included community nurse home visits, GP contacts, clinical nurse specialist visits, left ventricular ejection fraction monitoring and end of life care costs.

A complex patient access scheme (PAS) was proposed by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS

Scotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Without the PAS, for the base case comparison with capecitabine the submitting company estimated a cost per quality adjusted life year (QALY) of £96,185 based on an incremental cost of £87,177 and a QALY gain of 0.89. The sensitivity analysis showed that the results were most sensitive to the choice of parametric survival function and the OS estimates.

The following limitations were noted:

- The results are sensitive to the extrapolation approach used in the model. The company selected the gamma function to extrapolate the OS data over the time horizon of the model. While the reasons for selecting this function are clear, the median overall survival with trastuzumab emtansine (Kadcyla®) was slightly longer in the model than in the study. A more conservative approach which used the KM data and then fitted a gamma function to the tail of these data resulted in the incremental cost-effectiveness ratio (ICER) increasing to £105k. The SMC statistical advisor commented that this approach is likely to produce a more realistic estimate of OS.
- There are no direct data comparing trastuzumab emtansine (Kadcyla®) and capecitabine: therefore, a MTC was conducted to provide indirect evidence of the treatments' relative efficacy. In the resubmission, the use of a random-effects model resulted in wider credible intervals showing the range of uncertainty in the OS point estimates. The results were sensitive to using the 95% credible intervals of the HR for OS from the MTC as they included 1. This resulted in the ICER varying between £62k and dominated. However, the analysis which uses the upper 95% credible interval results in capecitabine being the more effective treatment, which lacks face validity given the results of the EMILIA study.
- The comparison with capecitabine is relevant, but SMC clinical experts also indicated trastuzumab used alone or off-label in combination with another chemotherapy agent (such as capecitabine, docetaxel or vinorelbine) are common treatment options. Lapatinib plus capecitabine was also mentioned as a treatment option in some patients but it was acknowledged that lapatinib is not recommended by SMC. Sensitivity analysis was provided comparing trastuzumab emtansine (Kadcyla®) with capecitabine plus trastuzumab, which resulted in a cost per QALY of £100k. A comparison with vinorelbine alone was also provided, which resulted in an ICER of £89k.

The Committee also considered the benefits of trastuzumab emtansine (Kadcyla®) in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission; a substantial improvement in quality of life; and the absence of other treatments of proven benefit. In addition, as trastuzumab emtansine (Kadcyla®) is an orphan-equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted trastuzumab emtansine (Kadcyla®) for use in NHS Scotland.

Additional information: guidelines and protocols

The European School of Oncology (ESO) and the European Society for Medical Oncology (ESMO) have published consensus guidelines: "ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)" in September 2014.[10] This guideline recommends that patients whose tumours progress on an anti-HER-2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER-2 therapy with subsequent treatment since it is beneficial to continue suppression of the HER-2 pathway. The optimal duration of anti-HER-2 therapy for metastatic breast cancer is currently unknown. In the case of progression on trastuzumab, the combination of trastuzumab plus lapatinib is also a reasonable treatment option in the course of the disease.

Healthcare Improvement Scotland (HIS) issued advice on 27 June 2012 that it has considered the National Institute for Health and Care Excellence (NICE) multiple technology appraisal (MTA) number 257: lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. The NICE guidance states that lapatinib or trastuzumab in combination with an aromatase inhibitor are not recommended for first-line treatment in postmenopausal women with metastatic hormone-receptor-positive breast cancer that over-expresses HER2. Postmenopausal women currently receiving lapatinib or trastuzumab in combination with an aromatase inhibitor should have the option to continue treatment until they and their clinicians consider it appropriate to stop. HIS advises that no important differences were identified for this NICE appraisal and the recommendations are as valid for Scotland as for England and Wales. The Scottish Medicines Consortium (SMC) has previously issued guidance to NHS Scotland on the use of lapatinib (768/12) and trastuzumab (386/07) in this indication (not recommended due to non-submission to SMC). This NICE MTA guidance supersedes the SMC advice.[6]

The National Institute for Health and Care Excellence (NICE) clinical guideline Advanced breast cancer: diagnosis and treatment (CG81) issued in February 2009 advises that patients who have previously received a taxane should be offered vinorelbine or capecitabine as second-line treatment and the other of the two agents as a third-line treatment.[5] It is recommended that patients receiving trastuzumab for advanced breast cancer should discontinue this at the time of disease progression outside the central nervous system. This guideline was updated in July 2014 but these recommendations are unchanged.

Additional information: comparators

Oral capecitabine, oral or intravenous vinorelbine. Off-label use of trastuzumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)
Trastuzumab emtansine (Kadcyla®)	**3.6mg/kg intravenously every three weeks**	**4,267**
Trastuzumab intravenous infusion	8mg/kg intravenously as a loading dose then 6mg/kg intravenously every three weeks	1,222 (1,630 for the loading dose)
Trastuzumab subcutaneous injection	600mg every three weeks	1,222
Vinorelbine	60mg/m^2* orally on day 1, 8 and 15 of a 21 day cycle	726
Vinorelbine	25 to 30mg/m^2 intravenously on day 1,8 and 15 of a 21 day cycle	420 to 509
Capecitabine	1,250mg/m^2 orally twice daily for 14 days of a 21 day cycle	223

Doses are for general comparison and do not imply therapeutic equivalence. Cost of capecitabine from eVadis on 3 November 2016 and costs of trastuzumab emtansine (Kadcyla®), trastuzumab and vinorelbine from eMIMS on 7 November 2016 and based on 70kg body weight and 1.8m^2 body surface area. *Oral vinorelbine dose can be increased to 80mg/m^2 after the first cycle if the neutrophil count allows, this dose would cost £924 per 21 day cycle. In the EMILIA study, the median time to progression was 9.6 months with trastuzumab emtansine (Kadcyla®): equating to 13 cycles which would cost £55,471. These costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there to be 100 patients eligible for treatment with trastuzumab emtansine (Kadcyla®) in year 1, rising to 139 in year 5, with an estimated uptake rate of 30% (30 patients) in year 1 and 70% (97 patients) in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

1. Trastuzumab emtansine (Kadcyla®) SPC. Roche Products Ltd. Electronic Medicines Compendium www.medicines.org.uk Last updated 11/02/2014

2. Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2-positive advanced breast cancer N Engl J Med 2012;367:1783-91

3. Krop IE, Kim S-B, Gonzalez-Martin A et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:689-99.

4. The European Medicines Agency (EMA) European Public Assessment Report. Trastuzumab emtansine (Kadcyla®) 19/09/2013, EMEA/H/C/002389/0000.

5. National Institute for Health and Care Excellence (NICE). Clinical Guideline 81. Advanced breast cancer. Diagnosis and treatment. 2009

6. Healthcare Improvement Scotland (HIS). Advice on NICE MTA number 257, June 2012

7. Dieras V, Miles D, Verma S et al. Trastuzumab emtansine (T-DM1) improves overall survival versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer: final results from the phase 3 EMILIA study. Abstract P4-14-01 presented at the San Antonio Breast Cancer Symposium; 2015.

8. Wildiers H, Kim S-B, Gonzalez-Martin A et al. Trastuzumab emtansine improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer: Final overall survival results from the phase 3 TH3RESA study. Abstract S5-05 presented at the San Antonio Breast Cancer Symposium; 2015.

9. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90.

10. Cardosa F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol 2014; doi:10.1093/annonc/mdu385

This assessment is based on data submitted by the applicant company up to and including 16 February 2017**.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS

Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.