trastuzumab, 600mg/5mL solution for injection (Herceptin®)  
SMC No. (928/13)
Roche Products Ltd

06 December 2013

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

**ADVICE:** following a full submission

**trastuzumab 600mg/5mL solution for injection (Herceptin®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** treatment of adult patients with HER2 positive metastatic breast cancer (MBC) and early breast cancer (EBC) in a range of settings (full details of licensed indication presented later in advice document).

Trastuzumab should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

**SMC restriction:** Subcutaneous trastuzumab injection is accepted for use in line with previous SMC advice for intravenous trastuzumab (this excludes its use in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab).

In a phase III randomised, open-label clinical study in patients with HER2-positive early breast cancer, subcutaneous trastuzumab was non-inferior to intravenous trastuzumab for the co-primary pharmacokinetic and efficacy endpoints of serum trough concentration ($C_{\text{trough}}$) at pre-dose cycle 8 before surgery and pathological complete response.

Overleaf is the detailed advice on this product.

**Vice Chairman,**
Scottish Medicines Consortium
**Indication**

*Metastatic breast cancer*

Trastuzumab is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

*Early breast cancer*

Trastuzumab is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.

Trastuzumab should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.¹

**Dosing Information**

600 mg/5mL irrespective of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously over 2-5 minutes every three weeks. Patients with MBC should be treated with trastuzumab until progression of disease. Patients with EBC should be treated with trastuzumab for one year or until disease recurrence whatever occurs first.¹

**Product availability date**

02 September 2013
Summary of evidence on comparative efficacy

Trastuzumab 600mg/5mL solution for injection is a new formulation of trastuzumab for subcutaneous (SC) injection. It is an alternative to trastuzumab intravenous infusion (IV) and is administered as a fixed dose. Trastuzumab is a recombinant humanised monoclonal IgG1 antibody which targets the human epidermal growth factor receptor 2 (HER2) and is used in the treatment of breast cancer which overexpresses this receptor (HER2-positive breast cancer). This new formulation also contains recombinant human hyaluronidase, an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. This allows the relatively large 5mL volume of trastuzumab to be given subcutaneously over a 2 to 5 minute period. The licensed indications for trastuzumab SC injection are identical to the breast cancer indications for trastuzumab IV.

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of trastuzumab SC for all of its licensed indications.

The clinical evidence derives principally from one phase III randomised, open-label, non-inferiority study (HannaH) to compare the pharmacokinetics, efficacy and safety of trastuzumab SC with trastuzumab IV in patients with HER2-positive early breast cancer. Eligible patients were aged ≥18 years with newly diagnosed HER2-positive non-metastatic primary invasive breast cancer. Patients were randomised equally to receive eight cycles of neoadjuvant chemotherapy administered concurrently with either trastuzumab SC or trastuzumab IV. Randomisation was stratified by disease stage and by oestrogen receptor status. Neoadjuvant chemotherapy consisted of four cycles of docetaxel (75mg/m²) every three weeks followed by four cycles of fluorouracil (500mg/m²), epirubicin (75mg/m²) and cyclophosphamide (500mg/m²) [FEC] every three weeks. Trastuzumab SC was given every three weeks at a fixed dose of 600mg in a volume of 5mL, injected into the thigh with a hand-held syringe over approximately 5 minutes. Trastuzumab IV was administered every three weeks according to the recommended dose (8mg/kg loading dose; 6mg/kg maintenance dose). Trastuzumab SC and IV were continued for 18 cycles (i.e. one year). Surgery was performed according to local practice after eight cycles of neoadjuvant therapy. In the adjuvant phase, radiotherapy and hormonal therapy were administered according to local practice. Blood samples were taken on day 1 of cycles 1 to 13 for pharmacokinetic analyses. The co-primary efficacy and pharmacokinetic outcomes were analysed in the per protocol population (n=260 for trastuzumab SC; n=263 for trastuzumab IV) using pre-specified non-inferiority margins.

The median duration of follow-up was 12.4 months in the trastuzumab SC group and 12.2 months in the trastuzumab IV group. The median dose intensity was 195.9mg/week in the trastuzumab SC group and 135.9mg/week in the trastuzumab IV group. In both treatment groups, the median relative dose intensity of all chemotherapy agents was 99%.

The co-primary pharmacokinetic endpoint was serum trough concentration of trastuzumab (C\textsubscript{trough}) measured at pre-dose cycle 8 before surgery, and the co-primary efficacy endpoint was pathological complete response (pCR) defined as the absence of invasive neoplastic cells in the breast. The geometric mean ratio of C\textsubscript{trough} subcutaneous/C\textsubscript{trough} intravenous was 1.33 (90% confidence interval [CI]: 1.24 to 1.44), with the lower limit of the 90% CI being greater than the prespecified non-inferiority margin of 0.8. pCR was achieved in 45% (118/260) of patients in the trastuzumab SC group and 41% (107/263) of patients in the trastuzumab IV group, corresponding to a difference (subcutaneous minus intravenous) of 4.7% (95% CI: -4.0 to 13.4), and the lower limit of the two-sided 95% CI for the difference was greater than the prespecified non-inferiority margin of -12.5%. Non-inferiority of
trastuzumab SC compared with trastuzumab IV was therefore demonstrated for both co-primary endpoints.

Sensitivity analysis in the intention-to-treat (ITT) population, found that pCR was achieved by 42% (124/294) of patients in the trastuzumab SC group and 37% (111/297) of patients in the trastuzumab IV group.\(^3\)

Secondary outcomes of the pharmacokinetic profile included exposure to trastuzumab, shown by values for the geometric mean area under the serum-concentration time curve from 0 to 21 days (AUC\(_{0\text{ to }21\text{ days}}\)), which was similar in both groups; ratio 1.07 (90% CI: 1.01 to 1.12).\(^3\)

Other efficacy secondary outcomes were total pathological complete response, defined as the absence of invasive neoplastic cells in the breast and ipsilateral lymph nodes. This was achieved in 39% (102/260) of patients in the trastuzumab SC group and 34% (90/263) of patients in the trastuzumab IV group; difference of 5% (95% CI: -3.5% to 14%).\(^3\) Time to response, defined as time from first drug administration to date of first clinical complete or partial response analysed in patients with measurable disease at baseline, gave a median of 6 weeks in both groups.\(^3\)

The supporting PrefHer study\(^4\) was a multicentre, open-label, randomised, cross-over study to evaluate patient preference for route of administration of trastuzumab in patients with HER2-positive non-metastatic primary breast cancer. It was a two cohort study, in Cohort 1 trastuzumab SC was administered via a single use injection (not yet licensed) and in Cohort 2 patients received trastuzumab SC via vial and syringe. Patients were randomised equally to receive four cycles of trastuzumab SC followed by four cycles of trastuzumab IV, or the reverse sequence (the cross-over period). After the cross-over period, patients continued to receive trastuzumab SC or IV to complete a total of 18 cycles. The primary outcome was the proportion of patients indicating an overall preference for the SC or IV route of administration, assessed by two study-specific telephone interviews. In the group who received trastuzumab SC first, 96% (112/117) of patients preferred the SC route of administration and 4.3% (5/117) of patients preferred the IV route. In patients who received trastuzumab IV first, 87% (104/119) of patients preferred the SC route, 9.2% (11/119) of patients preferred the IV route and 3.4% (4/119) of patients had no preference. The preference for trastuzumab SC was seen irrespective of whether patients had previously received trastuzumab (95% [54/57] patients or not 91% [162/179]). The two main reasons that patients gave for preferring the SC route were that it saved time or that it resulted in less pain and discomfort.\(^4\)

**Summary of evidence on comparative safety**

Overall, the adverse event profile of trastuzumab SC was similar to the known safety profile of trastuzumab IV.\(^3\) In the HannaH study, the proportion of adverse events of ≥grade 3 was the same in both treatment groups (52%).\(^3\) 17 patients in the trastuzumab SC group and 7 patients in the trastuzumab IV group withdrew from the study due to adverse events; the most common reason was LVEF dysfunction (5 patients in trastuzumab SC groups versus 2 patients in the trastuzumab IV group).

A greater proportion of serious adverse events was reported for trastuzumab SC (21% [62/297]) than trastuzumab IV (12% [37/298]) and this was mainly accounted for by differences in infections with or without neutropenia (8.1% [24/297] versus 4.4% [13/298]) and cardiac disorders (1.3% [4/297] versus 0.7% [2/298]).\(^1,3\) Other adverse events reported more frequently for trastuzumab SC than trastuzumab IV included administration-related reactions (48% versus 37%), hypertension (9.8% versus 4.7%) and post-operative wound infection (3.0% versus 1.7%).\(^1\)
Two patients in the trastuzumab SC group developed New York Heart Association (NYHA) class II heart failure, compared with none in the trastuzumab IV group; no patients developed NYHA class III or IV heart failure.3

As with trastuzumab IV, cardiac dysfunction and administration-related reactions (ARRs) may occur with trastuzumab SC. The summary of product characteristics recommends that patients should be observed for ARRs for 6 hours after the first injection and 2 hours after subsequent injections.1

### Summary of clinical effectiveness issues

Trastuzumab subcutaneous injection is a new formulation of trastuzumab that is presented as a ready to use liquid formulation that is administered as a fixed dose (600mg). It is an alternative to trastuzumab intravenous infusion, which has a variable dose according to patient weight. The submitting company has requested that the SMC considers the use of this product for all licensed indications. However, not all licensed breast cancer indications for trastuzumab have been accepted for use within NHS Scotland.

In the main phase III study (HannaH) in patients with HER2-positive, newly diagnosed primary breast cancer (stage I to IIIC), trastuzumab SC was non-inferior to trastuzumab IV for the co-primary efficacy and pharmacokinetic endpoints. Trastuzumab SC and trastuzumab IV were administered every three weeks concurrently with neoadjuvant chemotherapy consisting of four cycles of docetaxel (75mg/m²) every three weeks followed by four cycles of fluorouracil (500mg/m²), epirubicin (75mg/m²) and cyclophosphamide (500mg/m²) [FEC] every three weeks. The treatment regimen used in the pivotal study does not reflect current practice in Scotland, where docetaxel is usually administered after FEC. In addition, the Scottish Intercollegiate Guidelines Network (SIGN)5 recommends that patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy should receive trastuzumab either as adjuvant treatment or with non-anthracycline-based neoadjuvant chemotherapy, so it is uncertain whether trastuzumab would be used concurrently with anthracyclines in Scottish practice. There are limited clinical study data in patients who have received trastuzumab in combination with an anthracycline.

The main limitation of the HannaH study was that it only included patients with early breast cancer (EBC). There are no clinical study data available for trastuzumab SC in patients with metastatic breast cancer (MBC). However, since there are no clinically-relevant differences in the pharmacokinetics of trastuzumab in EBC and MBC at steady state, the European Medicines Agency (EMA) accepted the HannaH study to support the use of trastuzumab SC in both EBC and MBC.

Trastuzumab SC has advantages over trastuzumab IV in that it can be administered over a shorter time period (5 minutes compared with 30 minutes for intravenous trastuzumab [90 minutes for the loading dose]). Trastuzumab SC is administered as a fixed dose, so there is no need to calculate individualised doses and there is likely to be less waste compared with trastuzumab IV. The Hannah study showed comparable efficacy between trastuzumab SC and trastuzumab IV for all outcomes that were evaluated. Advantages to the service include less pharmacy time for preparation and less clinic time for administration.

In a supportive study (PrefHer), the majority of patients preferred SC administration of trastuzumab over IV administration.
Summary of comparative health economic evidence

The economic analysis submitted by the company was a cost-minimisation analysis (CMA) comparing trastuzumab SC with trastuzumab IV for the treatment of EBC and MBC in adult patients with HER2 positive breast cancer (as monotherapy or in combination with chemotherapy). A one year time horizon was used and the analysis was carried out from an NHS Scotland perspective. The comparator within the analysis contains the same active ingredient as the intervention, with the only difference between them being the method of administration. The comparator is appropriate.

The clinical evidence to support the CMA came primarily from the pivotal study, which demonstrated non-inferiority between trastuzumab SC and trastuzumab IV in EBC patients. For the purpose of the economic evaluation, the submitting company assumed the results of the EBC study also applied to MBC patients.

The economic analysis focussed on the relative costs per patient for trastuzumab SC versus trastuzumab IV. Costs included medicine acquisition costs and also non-medicine costs (i.e. administration costs, preparation costs or consumables). Due to the fact that trastuzumab IV dose is based on patients’ body weight, the submitting company used UK population weight distribution data to calculate the medicine costs associated with trastuzumab IV. Trastuzumab SC is a fixed dose treatment i.e. independent of body weight.

The base case results, for the overall analysis (medicine and non-medicine costs) were cost savings per EBC patient of £3,454.33 over a full 1-year treatment, and for MBC patients of £3,162.67 over a full 1-year treatment. Including medicine costs only, cost savings per patient per year were £1,441.75 and £1,239.53 for EBC and MBC respectively.

Sensitivity analyses (SA) were performed around the most important drivers. The above medicine cost savings included a reasonable assumption that trastuzumab IV administration would include 26% vial sharing, with the remaining 74% resulting in some wastage. Trastuzumab SC would not produce any wastage as it is administered as a fixed dose. The company’s sensitivity analysis showed that even if vial sharing for trastuzumab IV reached 70% and 62% for EBC and MBC patients respectively, trastuzumab SC would be associated with a lower medicine cost.

Another important variable that was analysed within the SA was patient weight. As mentioned above, trastuzumab IV is administered as a function of patients’ weight and, based on the relative price and dose requirements, SA showed that only patients weighing above 72kg would produce medicine cost savings. However, the non-medicine savings would still apply for the patients weighing less than 72kg and would offset any of the additional medicine costs.

The main uncertainty surrounding the analysis is that the assumption of comparable efficacy for MBC patients, which underpins the economic analysis, is not supported by data. However, on balance, the committee deemed the company’s approach to be reasonable. Therefore, the economic case for trastuzumab SC has been demonstrated.
Summary of patient and public involvement

Patient Interest Group Submissions were received from:
- Breast Cancer Care
- Breakthrough Breast Cancer

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline 134: Treatment of primary breast cancer (September 2013) recommends that adjuvant trastuzumab should be considered in all patients with HER2-positive breast cancer who receive adjuvant chemotherapy. Adjuvant trastuzumab should not be given concurrently with anthracyclines but may be given either concurrently with taxanes-based regimens or sequentially. Patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy should receive trastuzumab, either as adjuvant treatment or with non-anthracycline-based neoadjuvant chemotherapy.5

The National Institute for Health and Care Excellence (NICE) Clinical Guideline 80: Early and locally advanced breast cancer (February 2009) recommends trastuzumab given at 3 week intervals for one year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2-positive early breast cancer following surgery, chemotherapy, and radiotherapy when applicable.6

NICE Clinical Guideline 81: Advanced breast cancer (February 2009) states “For patients who are receiving treatment with trastuzumab for advanced breast cancer, discontinue treatment at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.” It states that randomised controlled trials are needed to assess whether patients who have had adjuvant trastuzumab should be offered further biological therapy.7

The European Society of Medical Oncology (ESMO) Clinical Practice Guidelines on Primary Breast Cancer (2013) state that trastuzumab in combination with chemotherapy in patients with HER2 overexpression/amplification approximately halves the recurrence risk and the recommended treatment duration is one year. Trastuzumab should not routinely be administered concomitantly with anthracyclines due to cardiotoxicity, but combination with taxanes is safe and has been demonstrated to be more effective than sequential treatment. Trastuzumab may be given in combination with radiotherapy and endocrine therapy.8

The ESMO Clinical Practice guidelines on locally recurrent or metastatic breast cancer (2012) recommend that anti-HER2 therapy (i.e. trastuzumab, lapatinib) in combination with chemotherapy, endocrine therapy or alone should be offered to all patients with HER2-positive metastatic breast cancer who do not have contra-indications for these treatments. These guidelines also state that continuing trastuzumab in combination with a different chemotherapy regimen after the first disease progression is superior to chemotherapy alone and that evidence suggests that anti-HER2 therapy should be continued for as long as possible.9
Additional information: comparators

Trastuzumab intravenous infusion.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per cycle (£)</th>
<th>Cost per course (£)</th>
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<tbody>
<tr>
<td>Trastuzumab subcutaneous injection</td>
<td>600mg every three weeks</td>
<td>1,222</td>
<td>22,000</td>
</tr>
<tr>
<td>Trastuzumab intravenous infusion</td>
<td>8mg/kg loading dose, then 6mg/kg every three weeks</td>
<td>1,222 (1,630 for the loading dose)</td>
<td>22,407</td>
</tr>
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Cost for trastuzumab intravenous infusion from MIMS on 17/09/13; cost for trastuzumab subcutaneous injection from the NHS dm+d website on 26/09/13; assumes a patient weight of 70kg and is the cost of the drug only based on full vials and not the volume administered. Assumes a course length of 18 cycles.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 493 for EBC patients and 198 for MBC patients in year 1 and in year 5, with an estimated uptake rate of 100% in all 5 years.

For EBC: The gross impact on the medicines budget was estimated to be £10.8m in year 1 and year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be savings of £24k in year 1 and year 5.

For MBC: The gross impact on the medicines budget was estimated to be £4.1m in year 1 and year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £6k in year 1 and year 5.
The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Trastuzumab Herceptin® 600mg/5mL solution for injection, summary of product characteristics, last updated 04/09/2013.
2. Trastuzumab Herceptin® 150mg powder for concentrate for solution for infusion, summary of product characteristics, last updated 26/02/2013.

This assessment is based on data submitted by the applicant company up to and including 15 November 2013.

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.

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.