

**AWMSG Secretariat Assessment Report – Advice no. 0312**  
**Trastuzumab (Herceptin<sup>®</sup>▼) 150 mg powder for**  
**concentrate for solution for infusion**

This assessment report is based on evidence from a limited submission by Roche Products Ltd on 7 September 2011.

**1.0 PRODUCT DETAILS**

<b>Licensed indication under consideration</b>	<p>Trastuzumab (Herceptin<sup>®</sup>▼) is indicated for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer<sup>1</sup>. This submission covers the licence extensions for treatment with trastuzumab:</p> <ul style="list-style-type: none"> <li>• following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel;</li> <li>• in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin<sup>1</sup>.</li> </ul> <p>Please see the Summary of Product Characteristics (SPC) for licensed indications not covered by this submission<sup>1</sup>.</p>
<b>Dosing</b>	<p>As a three-weekly regimen, the recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose<sup>1</sup>.</p> <p>As a weekly regimen, the recommended initial loading dose of 4 mg/kg should be followed by 2 mg/kg every week, administered concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide<sup>1</sup>.</p> <p>Please refer to the SPC (Section 5.1) for further information regarding chemotherapy combination dosing<sup>1</sup>.</p>
<b>Marketing authorisation date</b>	20 April 2011 <sup>2</sup> (initial licence for HER2-positive metastatic breast cancer received 28 August 2000 <sup>3</sup> ).

**2.0 DECISION CONTEXT**

**2.1 Background**

Breast cancer is the most common cancer in the UK<sup>4</sup>, and in 2009 there were 2,599 new cases of breast cancer in Wales<sup>5</sup>. It has been reported that 15–20% of breast cancers overexpress the receptor tyrosine kinase HER2<sup>6</sup>, which is involved in signal transduction pathways leading to cell growth and differentiation. HER2-positive tumours have a worse prognosis than HER2-negative tumours<sup>6,7</sup>; as such, HER2 overexpression serves as a marker of aggressive disease, and the receptor is a target for treatment<sup>6</sup>.

Trastuzumab is a recombinant, humanised IgG1 monoclonal antibody against HER2<sup>1</sup>. After binding, trastuzumab inhibits HER2, preventing proteolytic cleavage and activation, which induces apoptosis and decreases proliferation of HER2-overexpressing tumour cells<sup>6</sup>. Trastuzumab received a licence extension in

2006, which approved its use as a monotherapy for the treatment of HER2-positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy<sup>3</sup>. The licence extensions considered in this submission allow the use of trastuzumab concomitantly with a taxane following adjuvant anthracycline-containing chemotherapy, or the use of trastuzumab concomitantly with an anthracycline-free chemotherapy regimen<sup>2</sup>.

## 2.2 Comparators

The Welsh Medicines Partnership (WMP) requested chemotherapy with sequential trastuzumab as the comparator.

## 2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE) clinical guideline 80: Early and locally advanced breast cancer: diagnosis and treatment. 2009<sup>4</sup>. This guideline relates to the original licence for trastuzumab as a monotherapy, and supersedes NICE technology appraisal guidance 107: Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (2006)<sup>8</sup>.
- Scottish Intercollegiate Guidelines Network (SIGN) publication number 84: Management of breast cancer in women. A national clinical guideline. 2005<sup>9</sup>.
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Breast Cancer. 2011<sup>10</sup>.
- South West Wales Cancer Network: The management of breast cancer. 2011<sup>11</sup>.

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included brief details from three open-label, phase III clinical trials; National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) N9831, and Breast Cancer International Research Group (BCIRG) 006<sup>2</sup>.

### 3.1 NSABP B-31 and NCCTG N9831

The company submission included very limited results from NCCTG N9831 which compared treatment arms of chemotherapy with sequential trastuzumab and chemotherapy with concomitant trastuzumab: in one treatment arm, patients received adjuvant chemotherapy with doxorubicin (A) and cyclophosphamide (C) followed by paclitaxel (T) with concomitant trastuzumab (H) (AC→TH); and in another arm, patients received adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel with sequential trastuzumab (AC→T→H) (see Glossary). Trastuzumab was administered weekly, with an initial loading dose of 4 mg/kg, followed by 2 mg/kg for up to 52 weeks. Key inclusion criteria were adenocarcinoma of the breast with strongly positive HER2 overexpression, node-positive or high-risk node-negative disease, and complete resection of the primary breast tumour and axillary nodal dissection<sup>12</sup>. The primary endpoint was disease-free survival (DFS). Five-year analysis (available only in abstract format) showed a DFS of 84.2% for AC→TH (n = 954) compared with 79.8% for AC→T→H (n = 949), with a hazard ratio (HR) of 0.75 (p = 0.019; 95% confidence interval [CI]: 0.60–0.94)<sup>2,13</sup>.

The company also included results from a joint analysis of the NSABP B-31 and NCCTG N9831 treatment arms in which patients received adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel with or without concomitant trastuzumab (AC→TH and AC→T, respectively) (see Glossary)<sup>2,14</sup>. The combined analysis comprised 3,969 patients, and was balanced between AC→TH and AC→T treatment arms<sup>14</sup>. Follow-up at four years showed a DFS rate of 85.9% in patients that

received AC→TH, compared with 73.1% in patients that received AC→T. A HR of 0.49 was reported ( $p < 0.0001$ ; 95% CI: 0.41–0.58)<sup>2,14</sup>.

A safety analysis of NCCTG N9831 alone found that a higher proportion of patients receiving trastuzumab developed a cardiac event (congestive heart failure or cardiac death), but that the rate was comparable between trastuzumab-receiving arms: 0.3% for AC→T, 3.3% for AC→TH and 2.8% for AC→T→H<sup>2,15</sup>. No further safety data were provided by the company to compare concomitant (AC→TH) with sequential (AC→T→H) trastuzumab. The safety of AC→TH versus AC→T, was reported by the Committee for Medicinal Products for Human Use (CHMP), however this will not be discussed further as it does not compare chemotherapy with sequential trastuzumab to chemotherapy with concomitant trastuzumab<sup>16</sup>.

### 3.2 BCIRG 006

BCIRG 006 compared the efficacy and safety of doxorubicin and cyclophosphamide followed by docetaxel (AC→T); doxorubicin and cyclophosphamide followed by concomitant docetaxel and trastuzumab (AC→TH); and concomitant docetaxel, carboplatin and trastuzumab (DcarbH; anthracycline-free regimen) (see Glossary)<sup>17,18</sup>. This trial did not include a treatment arm in which patients received an anthracycline-free regimen with sequential trastuzumab. Trastuzumab (6 mg/kg) was administered as a 30-minute intravenous infusion every three weeks for one year<sup>16</sup>. Inclusion criteria were histologically proven breast cancer with HER2 amplification, definitive surgical treatment, and node-positive or high-risk node-negative disease. Patients were excluded if they had received prior systemic anti-cancer therapy, prior anthracycline therapy, prior radiation therapy or cardiac disease that would preclude the use of doxorubicin, docetaxel or trastuzumab<sup>16</sup>. Patients ( $n = 3222$ ) were randomised 1:1:1 to one of the three treatment arms and stratified by number of positive nodes: AC→T ( $n = 1072$ ), AC→TH ( $n = 1076$ ) and DcarbH ( $n = 1074$ )<sup>18</sup>. The primary endpoint was DFS, with OS measured as a secondary endpoint. Five-year follow-up data showed DFS of 75%, 84% and 81%, and OS of 87%, 92% and 91%, for the AC→T, AC→TH and DcarbH groups, respectively<sup>17</sup>.

### 3.3 WMP critique

- WMP requested chemotherapy with sequential trastuzumab as the comparator. Data from NCCTG N9831 was available to compare adjuvant chemotherapy (doxorubicin and cyclophosphamide) followed by paclitaxel with concomitant trastuzumab (AC→TH) with adjuvant chemotherapy (doxorubicin and cyclophosphamide), followed by paclitaxel with sequential trastuzumab (AC→T→H)<sup>2,13</sup>. However, BCIRG 006 did not include a treatment arm for anthracycline-free chemotherapy with sequential trastuzumab; therefore no comparison with an anthracycline-free with concomitant trastuzumab regimen (DcarbH) could be made.
- Limited cardiac safety data were provided by the company that compared adjuvant chemotherapy (doxorubicin and cyclophosphamide) followed by paclitaxel with concomitant trastuzumab (AC→TH) with adjuvant chemotherapy (doxorubicin and cyclophosphamide) followed by paclitaxel with sequential trastuzumab (AC→T→H). No further safety data were included in the submission.
- The company suggests that as trastuzumab may now be initiated earlier in the treatment regimen, the number of hospital visits required and the total treatment period is decreased<sup>2</sup>.
- No quality of life data have been provided by the company.

## **4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS**

### **4.1 Cost-effectiveness evidence**

Cost-effectiveness evidence is not required for a limited submission.

## **5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT**

### **5.1 Budget impact evidence**

#### **5.1.1 Context and methods**

The company estimates that there are up to 500 patients in Wales eligible for trastuzumab treatment each year, based on estimates from an All Wales Medicines Strategy Group (AWMSG) briefing note from 2006<sup>19</sup>. The company anticipates that cost savings will result from the concomitant administration of trastuzumab with chemotherapy, as a result of fewer overall outpatient visits for drug administration<sup>2</sup>. Irrespective of whether taxanes are given once-weekly or three times weekly, the company anticipates concomitant administration of trastuzumab will save four outpatient attendances and will shorten overall treatment duration by 12 weeks compared with sequential administration as stipulated in the original licensed indication (anthracycline regimen followed by taxanes given every three weeks followed by trastuzumab). Concomitant administration of trastuzumab with a non-anthracycline regimen is anticipated to save eight outpatient visits compared with the original licensed indication. Using an outpatient chemotherapy delivery cost of £237<sup>20</sup>, the company-estimated cost savings for the two above regimens are £948 and £1,896, respectively. If applied to all the anticipated 500 eligible patients in Wales, this would equate to a maximum cost saving of £474,000 if trastuzumab was to be co-administered with taxanes following anthracycline treatment, and £948,000 if trastuzumab was to be co-administered with the non-anthracycline regimen.

The company also notes greater patient convenience and lower costs associated with fewer outpatient visits.

#### **5.1.3 WMP critique**

The company adopted a simple costing analysis based on administration costs. Concomitant administration of trastuzumab was associated with a greater incidence of cardiac adverse events, in particular heart failure<sup>16</sup>, which was not accounted for in the company's overall cost estimates. Data regarding long-term cardiac effects are limited, and long-term cardiac monitoring is required. The company has subsequently provided supplementary cost estimates for the impact of increased episodes of heart failure associated with concomitant administration of trastuzumab. Based on average English NHS reference costs for non-elective short stay associated with heart failure, the additional 1.3% to 1.4% of patients found in clinical trials to experience heart failure with concomitant administration of trastuzumab<sup>15</sup> is estimated by the company to result in an additional cost of around £7 per patient treated, which the company notes is more than offset by the average per patient administration cost savings associated with concomitant administration of trastuzumab. In addition, concomitant administration also appears to have resulted in small but significant improvements in disease-free survival, which conservatively are not included in the company's cost analysis.

Estimates of eligible patient numbers are dated and the company notes that the new licensed indication permits use of trastuzumab in patients who, due to their cardiac profile, are not candidates for anthracycline-based regimens, or patients who may not be eligible for trastuzumab after anthracycline therapy<sup>2</sup>. The number of patients likely to be treated each year, and consequently the maximum costs savings reported above, are therefore subject to some uncertainty.

## 5.2 Comparative unit costs

Table 1 shows examples of trastuzumab acquisition costs for the treatment of a 70 kg patient with HER2-positive early breast cancer. The costs of other chemotherapy regimens are not included.

**Table 1. Examples of trastuzumab acquisition costs for the treatment of patients with HER2-positive early breast cancer.**

Drug	Regimen	Cost per 70 kg patient including vial wastage
Trastuzumab (Herceptin <sup>®</sup> ) 150 mg vial	1. Loading dose of 8 mg/kg followed by maintenance dose of 6 mg/kg every 3 weeks for a further 51 weeks	£21,185
	2. Loading dose of 4 mg/kg followed by maintenance dose of 2 mg/kg every week for a further 51 weeks	£20,370

*Costs are based on MIMS list prices<sup>21</sup>.  
This table does not imply therapeutic equivalence of drugs or the stated doses.*

## 6.0 ADDITIONAL INFORMATION

### 6.1 Shared care arrangements

WMP is of the opinion that trastuzumab is not suitable for shared care within NHS Wales.

## GLOSSARY

**Table 2. Treatment regimens used in trials NSABP B-31, NCCTG N9831 and BCIRG 006.**

Treatment arm	Regimen
AC→T	Adjuvant doxorubicin and cyclophosphamide, followed by a taxane
AC→TH	Adjuvant doxorubicin and cyclophosphamide, followed by a taxane with <b>concomitant</b> trastuzumab
AC→T→H	Adjuvant doxorubicin and cyclophosphamide, followed by a taxane with <b>sequential</b> trastuzumab
DcarbH*	Concomitant docetaxel, carboplatin and trastuzumab*
* Anthracycline-free regimen A = doxorubicin; C = cyclophosphamide; carb = carboplatin; D = docetaxel; H = trastuzumab; T = taxane (e.g. paclitaxel or docetaxel)	

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