PUBLIC SUMMARY DOCUMENT

Product: Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®

Sponsor: Roche Products Pty Limited

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought an authority required PBS listing for the treatment of patients with HER2 positive early breast cancer following surgery in association with chemotherapy.

2. Background

The PBAC had not previously considered a submission from the sponsor for listing the product for early breast cancer.

3. Registration Status

Trastuzumab was registered on 4 September 2000 for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

- in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or
- as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease.

Trastuzumab was registered on 21 April 2006 for the treatment of patients with HER2 positive localised breast cancer in association with chemotherapy.

Localised means node-positive disease, or node negative disease with a tumour diameter greater than 20mm.

4. Listing requested and PBAC's View

Authority required
Initial treatment for HER2 positive localised breast cancer, in patients with node positive disease, or node negative disease with a primary tumour diameter greater than 20mm, in association with chemotherapy. HER2 positivity requires demonstration of 2+ or 3+ staining by immunohistochemistry (on a scale of 0, 1+, 2+, 3+) and subsequent confirmation of HER2 positivity by in situ hybridisation (ISH).

Continuing treatment for HER2 positive localised breast cancer, where the patient has previously been issued with an authority prescription for initial treatment with this drug.

The treatment course is limited to 52 weeks.

The PBAC considered trastuzumab should be subsidised for up to 52 weeks of treatment in HER2 positive early breast cancer patients with specified cardiac function.

The PBAC's view was that women with HER2 positive disease who are receiving chemotherapy when any listing takes effect, or who are already purchasing the drug privately, should qualify for subsidy from the date of listing.

See also Recommendation and Reasons

5. Clinical place for the proposed therapy

Among females, breast cancer is the most frequently diagnosed cancer and it is the most common cause of cancer-related death. Surgery is the main modality of local treatment for breast cancer. Surgery and/or radiotherapy can control locoregional disease in a large proportion of patients.

Adjuvant systemic therapy is defined as the administration of chemotherapy or hormonal therapy after primary surgery for breast cancer in order to control clinically occult micro-metastases. The aim of adjuvant chemotherapy is to treat undetectable cancer cells, to reduce the risk of cancer recurrence, and thereby improve survival.

Because systemic adjuvant therapies have been proven effective, they should be considered in the management of all women with high or moderate risk of recurrence after local therapy for early breast cancer. The choice of treatment for early breast cancer depends on a patients' risk category and their responsiveness to endocrine therapies.

HER2 overexpression has been confirmed as an adverse prognostic factor and a predictive factor for response to trastuzumab. Trastuzumab is a recombinant humanised monoclonal antibody that specifically targets the epidermal growth factor receptor (HER2) protein.

6. Comparator

The submission appropriately nominated placebo as the comparator.

7. Clinical Trials

The PBAC considered the results from five randomised, controlled trials of trastuzumab in early breast cancer. The trials published at the time of the submission were as follows:

Trial/First author	Protocol/Publication title	Publication citation
Piccart-Gebhart M (HERA trial)	Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.	New England Journal of Medicine 2005, 353: 1659-1672.
Romond E (US NCI trial B-31)	Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.	New England Journal of Medicine 2005, 353: 1673-1684.
Romond E (US NCI trial N9831) *	Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.	New England Journal of Medicine 2005, 353: 1673-1684.
Joensuu H (FinHer trial)	Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.	New England Journal of Medicine 2006, 354: 809-820.
Slamon D (BCIRG 006)	Phase III randomised trial comparing doxorubicin and	San Antonio Breast Cancer Conference, December 2005.

	cyclophosphamide followed by docetaxel (AC→T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study.	

* The results from an exploratory interim analysis of the treatment arm of US NCI trial N9831, in which trastuzumab was administered sequentially to chemotherapy (ie, after paclitaxel), were located during the evaluation (Slide presentation by Edith Perez at May 2005 American Society of Clinical Oncology [ASCO] Annual Meeting. Abstract 556). These results have not been published in a peer-reviewed journal.

8. Results of Trials

For the primary interim analysis of disease-free survival, a statistically significant difference favouring trastuzumab administered sequential to chemotherapy for 1 year compared to observation alone was observed in the HERA trial (hazard ratio [HR] at 2 years: 0.54; 95%CI 0.43, 0.67). However, no statistically significant difference between trastuzumab administered sequentially to paclitaxel and paclitaxel alone was observed in the US NCI trial N9831 (HR: 0.87; 95%CI: 0.67, 1.13). Statistically significant reductions in the risk of a DFS event favouring trastuzumab were reported by the interim analyses of other trials (HR for joint analysis of B-31 and N9831 = 0.48 [95%CI: 0.39, 0.59]; HR for FinHer trial = 0.42 [95%CI: 0.21, 0.83]; HR for BCIRG 006 =0.49 [95%CI: 0.37, 0.65]).

No statistically significant difference was detected in the hazard ratios for overall survival in the 12-month analysis of HERA or the FinHer trial. The 23-month analysis of HERA, provided prior to PBAC's consideration, showed that overall survival with sequential trastuzumab, compared with observation, was statistically significant (HR 0.66; 95% CI: 0.47, 0.91; p=0.0115). Although the hazard ratio for the joint analysis of B-31 and N9831 was reported to be significant (0.67, p=0.0136), the p-value did not cross the pre-specified formal boundary of p=0.0000015 required for statistical significance.

Trastuzumab was generally associated with a higher incidence of toxicities compared to no trastuzumab. The more commonly reported adverse events include infusion-related toxicities (eg, headache and fatigue), musculoskeletal pain (eg, arthralgia), infections (eg, nasopharyngitis and influenza), haematological abnormalities (eg, neutropenia), pulmonary toxicities (eg, dyspnoea) and gastrointestinal disturbances (eg, diarrhoea).

For HERA, a statistically significantly greater risk of cardiac events was observed in trastuzumab-treated patients compared with patients managed by observation (RR = 10.2; 95% CI: 1.3 – 79.4). Similarly, a significantly higher risk of cardiac events (ie, symptomatic CHF and cardiac death) was observed for trastuzumab-treated patients compared with the control arm by the joint analysis of the US NCI trials (RR = 4.8, 95%CI: 2.5 – 9.2). Trastuzumab was associated with a statistically significantly greater risk of LVEF decline when compared to patients not on trastuzumab in HERA and the joint analysis of B-31 and N9832. Inconclusive results with respect to cardiac endpoints were reported for the BCIRG trial – in the arm where trastuzumab was administered with carboplatin, there was no statistically significant difference for trastuzumab versus control

patients. However, where trastuzumab was administered without carboplatin, there was significantly more cardiac toxicity in the trastuzumab-treated group compared with the control group. No statistically significant difference between the trastuzumab-treated group and the control group in rate of cardiac events or in left ventricular function was observed in the FinHer trial (which administered once-weekly trastuzumab for only 9 weeks).

9. Clinical Claim

The submission claimed that trastuzumab given either sequentially or concurrently with adjuvant chemotherapy had significant advantages in effectiveness over adjuvant chemotherapy alone but was associated with greater toxicity.

The PBAC concluded that based on the totality of evidence currently available, treatment with trastuzumab should be restricted to commence concurrently with adjuvant chemotherapy. The Committee also agreed that trastuzumab should not be used in patients with a left ventricular ejection fraction (LVEF) < 45% and/or in those with symptomatic heart failure.

See also Recommendation and Reasons

10. Economic Analysis

Two preliminary economic evaluations were presented. The choice of the cost-effectiveness approach was valid. The resources included were drug costs, costs associated with administration, and costs of monitoring patients. The trial-based incremental discounted cost per extra disease-free year gained was > $200,000 over 3 years (based on the HERA trial); and in the range $105,000 - $200,000 over 4.69 years (based on the US NCI trials).

A modelled economic evaluation was presented. The choice of the cost-effectiveness approach was valid. The resources included were drug costs, drug administration costs, costs associated with monitoring of patients, costs for managing subsequent events including recurrence (locoregional and distant) and CHF. The base case modelled incremental discounted cost per extra QALY gained over 40 years was in the range of $15,000 - $45,000.

Prior to the PBAC consideration, additional sensitivity analyses were conducted. The analyses assumed the hazard ratio observed in the trial would apply for 5 years but that beyond that time the curves for proportion of patients with progression of disease will be parallel. The incremental discounted costs per extra QALY gained over 40 years was in the range of $45,000 - $75,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was < 10,000, while the financial cost per year to the PBS was > $100 million in Year 1 following listing.

12. Recommendation and Reasons

The PBAC recommended listing for the treatment for HER2 positive early breast cancer commencing concurrently with adjuvant chemotherapy following surgery on a cost-effectiveness basis over no treatment. The PBAC considered that, disease recurrence would be reduced by around 30% in individuals with HER2 gene amplified early breast cancer. This conclusion was based on the available evidence which included short-term follow up data combined with a prediction of effects over the longer term (40 years). This estimate is based upon the hazard ratio (HR=0.48 for concurrent therapy) observed in the clinical trials being assumed in the model to persist for 5 years after initiation of therapy and then to revert to 1, apportioned over a total period of 40 years. This assessment may change as more evidence becomes available. The PBAC further recommended that women with HER2 positive disease who are receiving chemotherapy when any listing takes effect, or who are already purchasing the drug privately, should qualify for subsidy from the date of listing.

The PBAC concluded that the optimal chemotherapy partner for trastuzumab is unknown, and that based on the totality of evidence currently available, treatment with trastuzumab should commence concurrently with adjuvant chemotherapy.

The PBAC noted that the trials presented in the submission used different adjuvant chemotherapy regimens and in some trials (HERA, one arm of N9831) trastuzumab was administered sequentially to chemotherapy, while in others (B-31, BCIRG006, one arm of N9831) trastuzumab was commenced concurrently with chemotherapy. With the exception of the sequential trastuzumab treatment arm of N9831, a statistically significantly higher disease-free survival (DFS) was observed in all trials for trastuzumab-treated patients compared with patients not receiving trastuzumab. No statistically significant difference in DFS was observed in the sequential trastuzumab treatment arm of N9831 compared with the paclitaxel alone arm. In addition to not being statistically significant, the magnitude of the treatment effect in DFS observed in the N9831 comparison is substantially lower than that observed in the HERA trial (HR: 0.87 vs. 0.54 respectively). The PBAC found it difficult to resolve the apparent inconsistency between the two sets of results.

The Committee further noted that there is some evidence to indicate that certain chemotherapy is a treatment effect modifier of trastuzumab. This may occur indirectly with those cytotoxic agents where HER2 gene amplification is a treatment effect modifier, such as anthracyclines (NEJM; 2006; 354:2103-2111). Some chemotherapy agents interact directly with trastuzumab both in vitro and in vivo (metastatic disease). This interaction may be synergistic eg. vinorelbine, docetaxel, carboplatin, etoposide; additive eg. paclitaxel, doxorubicin, vinblastine, methotrexate or antagonistic: eg 5 fluorouracil. The HERA protocol allowed adjuvant chemotherapy at the investigators choice. This was not taken into account in the subsequent randomization to treatment and may have influenced subsequent responsiveness to trastuzumab.

The PBAC noted the ESC advice that the clinical trials available to date suggest that there is no evidence of an efficacy advantage between trastuzumab administered for one year as proposed by the submission compared with trastuzumab administered every week for 9 weeks in the FinHer trial. However the Committee agreed that, although this is a reasonable hypothesis, the FinHer data can be criticised on the grounds that the difference in overall survival is not significant, the results are based on a small pre-specified sub-study of 231 patients, the event numbers are small and the upper age limit is lower than in

other studies, the last two of which may also have contributed to the reduced the rate of cardiac toxicity observed. Additionally, the results of FinHer could not be independently validated as all other available studies use prolonged treatment with trastuzumab.

Overall the Committee considered that the optimal duration of therapy with trastuzumab is unknown, but that the currently available evidence supports 52 weeks.

The PBAC considered it essential that all patients commencing therapy with trastuzumab have demonstrated HER2 gene amplification as determined by a histopathologist using an appropriately validated assay. This is due to the high incidence of false positive and false negative results when HER2 status is determined by immunostaining, together with safety concerns necessitating accurate targeting of the drug to the population most likely to benefit. The PBAC recommended that Roche be requested to provide an accessible gene amplification test to determine HER2 positivity free of charge, pending consideration of Medicare funding by the Medical Services Advisory Committee.

The Committee agreed that trastuzumab should not be used in patients with a left ventricular ejection fraction (LVEF) < 45% and/or in those with symptomatic heart failure. The PBAC noted that patients with these conditions were excluded from the trials, that use in these patient groups is contraindicated in the TGA Product Information and that substantial safety concerns had been raised in relation to heart damage.

The major issue of concern to the PBAC with respect to the economic analyses presented in the submission was the assumption that the hazard ratio (HR) observed at two/three years remains the same for the 40-year duration of the model. The PBAC did not accept this assumption, noting comments from the 2000 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview that the main effect on recurrence for polychemotherapy is seen in the first five years after which time (until 15 years at least) the curves become parallel, and that the proportional reduction in recurrence will tend to be systematically greater in the early results from new trials than when those same trials mature. If the model for concurrent administration is rerun with the assumption that the HR remains constant for 5 years and then reverts to one, the incremental cost per extra quality adjusted life year is in the range of $45,000 - $75,000.

A final issue of concern to PBAC was the overall cost to Government of listing trastuzumab on the PBS for HER2 positive early breast cancer. If it is assumed that around 25% of all patients diagnosed with early breast cancer will test positive for HER2 gene amplification using appropriate validated assays, and that 90% of these patients will take up treatment, the cost to Government might be more than $100 million in Year 1 of listing. Epidemiological sources report that between 15% and 25% of early breast cancer patients may test positive for HER2 gene amplification.

Recommendation

Section 100 Special Authority Program

TRASTUZUMAB

NOTE:

Any queries concerning the arrangements to prescribe trastuzumab may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Written applications for authority to prescribe trastuzumab should be forwarded

to: Medicare Australia Prior Written Approval of Specialised Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001 Further prescribing information is on the Medicare Australia website at www.medicareaustralia.gov.au.

Section 100 authority required

Initial treatment for HER2 positive early breast cancer commencing concurrently with adjuvant chemotherapy following surgery. The total duration of PBS-subsidised treatment (initial plus continuing) that will be authorised is 52 weeks. HER2 positivity must be demonstrated by in situ hybridisation (ISH). Trastuzumab must not be used in patients with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure. Cardiac function must be tested by a suitable method including, for example, ECHO or MUGA, prior to seeking the initial authority approval and then at 3 monthly intervals during treatment. Authority applications for initial treatment must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Early Breast Cancer - PBS Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes: (i) a copy of the pathology report from an Approved Pathology Authority confirming the presence of HER2 gene amplification by in situ hybridisation (ISH); and (ii) a copy of the signed patient acknowledgement form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)]. The medical practitioner should request sufficient quantity based on the weight of the patient to provide for a maximum of 3 weeks' treatment (equivalent to the loading dose for the 3 weekly regimen, and the loading dose and 2 weekly doses for the once weekly regimen).

Section 100 authority required

Initial treatment for HER2 positive early breast cancer in patients receiving treatment with adjuvant chemotherapy following surgery at 1 October 2006. The total duration of PBS-subsidised treatment (initial plus continuing) that will be authorised is 52 weeks. HER2 positivity must be demonstrated by in situ hybridisation (ISH). Trastuzumab must not be used in patients with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure. Cardiac function must be tested by a suitable method including, for example, ECHO or MUGA, prior to seeking the initial authority approval and then at 3 monthly intervals during treatment. Authority applications for initial treatment must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Early Breast Cancer - PBS Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes: (i) a copy of the pathology report from an Approved Pathology Authority confirming the presence of HER2 gene amplification by in situ hybridisation (ISH); and

(ii) a copy of the signed patient acknowledgement form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)]. The medical practitioner should request sufficient quantity based on the weight of the patient to provide for a maximum of 3 weeks' treatment (equivalent to the loading dose for the 3 weekly regimen, and the loading dose and 2 weekly doses for the once weekly regimen).

Section 100 authority required

Initial PBS-subsidised treatment for HER2 positive early breast cancer where the patient was receiving treatment with trastuzumab at 1 October 2006. The patient is eligible to receive sufficient trastuzumab to complete 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy. Trastuzumab must not be used in patients with a left

ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure. Cardiac function must be tested by a suitable method including, for example, ECHO or MUGA, at 3 monthly intervals during treatment. Authority applications for initial PBS-subsidised treatment must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Early Breast Cancer - PBS Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes: (i) the date upon which the patient commenced non-PBS-subsidised treatment with trastuzumab and the number of weeks of treatment received; and (ii) a copy of the signed patient acknowledgement form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)]. The medical practitioner should request sufficient quantity based on the weight of the patient for 3 weeks' supply (equivalent to 1 dose for the 3 weekly regimen, or 3 doses for the once weekly regimen). Up to a maximum of 3 repeats may be authorised.

Section 100 authority required
Continuing treatment for HER2 positive early breast cancer where the patient has previously received treatment with PBS-subsidised trastuzumab. The patient is eligible to receive sufficient trastuzumab to complete 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy. Trastuzumab must not be used in patients with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure. Cardiac function must be tested by a suitable method including, for example, ECHO or MUGA, at 3 monthly intervals during treatment. Authority applications for continuing treatment may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). The medical practitioner should request sufficient quantity based on the weight of the patient for 3 weeks' supply (equivalent to 1 dose for the 3 weekly dosing regimen, or 3 doses for the once weekly dosing regimen). Up to a maximum of 3 repeats may be authorised.

Maximum quantity: 1

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment
No comment.