**PUBLIC SUMMARY DOCUMENT**
**Product:** Trastuzumab, powder for I.V. infusion, 60 mg and 150 mg, Herceptin®
**Sponsor:** Roche Products Pty Ltd
**Date of PBAC Consideration:** November 2012

## 1. Purpose of Application

The major re-submission sought an extension to the current Section 100 (Efficient Funding of Chemotherapy) Private Hospital Authority Required and Public Hospital/Clinic Authority Required (Streamlined) listing to include the treatment of human epidermal growth factor receptor 2 (HER2) positive, advanced (equivalent stage III or IV) adenocarcinoma of the stomach or gastro oesophageal junction, in patients who have not received prior treatment for advanced disease, in combination with cisplatin and either capecitabine or 5 fluorouracil, with a WHO performance status of 2 or less and who does not have progressive disease.

## 2. Background

Trastuzumab for this indication was previously considered by the PBAC at the July 2011 meeting but listing was rejected on the basis of unacceptably high and uncertain incremental cost-effectiveness ratios.

*See the July 2011 trastuzumab Public Summary Document for further information.*

Trastuzumab is currently available on the PBS for the treatment of early and advanced HER2 positive breast cancer.

## 3. Registration Status

The TGA registration of trastuzumab 150 mg was extended on 17 September 2010 to include the new indication:

"For use in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease."

Trastuzumab is also TGA indicated for:
Treatment of patients with HER2 positive localised breast cancer following surgery and in association with chemotherapy and, if applicable, radiotherapy.
Treatment of patients with metastatic breast cancer who have tumours that over express HER2:

- as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;
- in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or
- in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

Trastuzumab powder for injection 60 mg was TGA registered for the above indications on 3 December 2010.

## 4. Listing Requested and PBAC's View

Section 100 – EFFICIENT FUNDING OF CHEMOTHERAPY
Authority required
Initial treatment for HER2 positive advanced (equivalent to stage III or IV) adenocarcinoma of the stomach or gastro-oesophageal junction, in patients who have not received prior treatment for advanced disease, in combination with cisplatin and either capecitabine or 5 fluorouracil, with a WHO performance status of 2 or less.

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.

*The submission proposed the following 6 scenarios for testing HER2 status for inclusion in the restriction to determine eligibility for PBS-subsidised treatment with trastuzumab, with scenario 5 (shown in bold) the submission's preferred choice:*

Scenario 1(Decision Analytic Protocol (DAP) base case)
Immunohistochemical (IHC) evidence of HER2 overexpression as described by a 0, 1+, 2+ or 3+
IHC score, subsequently confirmed as exhibiting HER2 gene amplification by in situ hybridisation (ISH).

Scenario 2(ToGA intention-to-treat (ITT) population)
Immunohistochemical (IHC) evidence of HER2 overexpression as described by a 3+ IHC score. For cases with a score of less than 3+ by IHC, confirmation of HER2 positive status by ISH is mandatory.

Scenario 3 (High HER2)
Immunohistochemical (IHC) evidence of HER2 overexpression as described by a 2+ IHC score, subsequently confirmed as exhibiting HER2 gene amplification by in situ hybridisation (ISH). Immunohistochemical (IHC) evidence of HER2 overexpression at the 3+ level.

Scenario 4 (IHC 3+)
Immunohistochemical (IHC) evidence of HER2 overexpression as described by a 3+ IHC score.

**Scenario 5 (resubmission base case)**
**Immunohistochemical (IHC) evidence of HER2 overexpression as described by a 2+ or 3+ IHC score, subsequently confirmed as exhibiting HER2 gene amplification by in situ hybridisation (ISH).**

Scenario 6 (IHC 3+/ISH+)
Immunohistochemical (IHC) evidence of HER2 overexpression as described by a 3+ IHC score, subsequently confirmed as exhibiting HER2 gene amplification by in situ hybridisation (ISH).

Section 100 – EFFICIENT FUNDING OF CHEMOTHERAPY
Authority required

Continuing treatment for HER2 positive advanced (equivalent to stage III or IV) adenocarcinoma of the stomach or gastro-oesophageal junction in combination with cisplatin and either capecitabine or 5-fluorouracil, where the patient has previously received treatment with PBS-subsidised trastuzumab and who does not have progressive disease.

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.

*For PBAC's view, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy

Currently, approved chemotherapy regimens for advanced gastric cancer include triplet regimens epirubicin + cisplatin + capecitabine (ECX) or 5-FU (ECF), and doublet regimens cisplatin + capecitabine (CX) or cisplatin + 5-FU (CF).

Trastuzumab, in combination with chemotherapy, was proposed as an alternative first-line treatment option for HER2 positive advanced gastric cancer.

## 6. Comparator

The resubmission nominated treatment with cisplatin and either 5-FU or capecitabine (CF) (i.e. the comparator in the main clinical trial, ToGA) as the comparator despite treatment with epirubicin, cisplatin and either 5-FU or capecitabine (ECF) being the standard treatment in patients with advanced gastric cancer. The justification for the selection was that the body of clinical evidence and Australian and international expert opinion suggested there to be no overall survival benefit from the addition of epirubicin to CF, citing Pozzo and Ohashi (2009), Yun et al. (2010) and Price et al. (2012) as evidence of no difference in treatment effect. Therefore, CF was assumed by the submission to be a valid proxy for ECF.

*For PBAC's view, see Recommendation and Reasons.*

## 7. Clinical Trials

No new trial of the effectiveness of trastuzumab was reported in the resubmission, compared with the previous submission. ToGA (published as Bang, et al. 2010) was a randomised open-label trial, that compared trastuzumab (8 mg/kg intravenous (IV) loading dose on day one followed by 6 mg/kg IV infusion once every three weeks) in combination with cisplatin (80 mg/m$^2$ IV infusion on day 1) and a fluoropyrimidine (either capecitabine (1,000 mg/m$^2$ orally twice daily for 14 days) or 5-FU (800 mg/m$^2$/day IV infusion over five days)) to the same regimen of doublet chemotherapy alone (CF), as first-line therapy in patients with HER2-positive advanced gastric cancer. The primary outcome was overall survival, although progression-free survival was also reported and used in the economic evaluation. No evidence was provided in the resubmission concerning the effectiveness of trastuzumab in HER2 negative patients with advanced gastric cancer.

Details of the ToGA trial have been published in the July 2011 trastuzumab Public Summary Document.

## 8. Results of Trials

The overall survival (OS) results for Scenario 2 (TOGA ITT population), Scenario 3 ('High' HER2 subgroup) and Scenario 4 (IHC 3+ subgroup) are reported in the July 2011 trastuzumab Public Summary Document and correspond to Scenario 1, Scenario 2 and Scenario 3 referred to in the July 2011 Public Summary Document. OS results for Scenarios 1, 5 and 6 were consistent with those for Scenarios 2, 3 and 4.

Results for progression free survival (PFS) for all scenarios were consistent with the results for OS.

The adverse event profiles for HCF (trastuzuamb, cisplatin and fluoropyrimidine) and CF (cisplatin and fluoropyrimidine) under Scenario 5 (i.e. the resubmission base case) were comparable and suggested that the addition of trastuzumab to CF did not adversely affect the safety profile of the chemotherapy regimen. The adverse event profiles for HCF and CF under the other five testing scenarios demonstrated a similar pattern.

*For PBAC's view, see Recommendation and Reasons.*

## 9. Clinical Claim

The resubmission described trastuzumab in combination with CF chemotherapy as superior, compared to CF chemotherapy alone, in terms of comparative effectiveness and as no worse than CF in terms of comparative safety in advanced gastric cancer patients who have been tested as HER2 positive by IHC and/or ISH.

*For PBAC's view, see Recommendation and Reasons.*

## 10. Economic Analysis

The resubmission presented a cost-utility/cost-effectiveness analysis based on the claimed clinical superiority of adding trastuzumab. The resubmission presents an incremental cost-effectiveness ratio (ICER) in the range of $45,000 - $75,000 per quality adjusted life year (QALY) gained (resubmission base case), based on efficacy data from the ToGA trial, applied to HER2 positive patients in the proposed and comparator arms and extrapolated to 5 years. Utility weights gathered in ToGA and from literature (Curran, et al. 2009) were applied. Drug usage was estimated from both the ToGA trial and market research data were used to determine the proportion of patients in the comparator arm that receive CF/ECF.

*For PBAC's view, see Recommendation and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

For all six scenarios presented in the resubmission, the likely number of patients per year was estimated in the submission to be less than 1,000 in Year 5, at an estimated net cost per year to the Government of less than $4 million in Year 5.

*For PBAC's view, see Recommendation and Reasons.*

## 12. Recommendation and Reasons

The PBAC deferred consideration of this application to obtain advice, including from MSAC, on the optimal algorithm for implementing HER2 testing in Australia. This advice should

include information regarding the best practice to obtain high rates of satisfactory tissue specimens and the role of centralised pathology testing where both immunohistochemistry (IHC) and in situ hybridisation (ISH) was undertaken in the same laboratory. It would also be helpful for MSAC to comment on the role of quality assurance in specifying minimal training and test performance characteristics such as the test strategy, the scoring system, and the type of ISH test. Clarification was also sought on when to test, with reference to when to treat, the implications of tumour heterogeneity on testing outcomes, and the stability of HER2 status between primary tumours and metastases.

If a HER2 testing process could be implemented, MSAC's advice was also sought on whether this testing process would provide sufficient confidence in the results of these tests to guide trastuzumab treatment decisions.

The PBAC also requested advice from MSAC on the following matters for the various test strategies proposed in the resubmission:

- the prevalence of HER2 positivity in Australian patients with gastric and gastro-oesophageal cancer;
- the number of tests per patient treated with trastuzumab, which should reflect the frequency of repeat testing under the proposed optimisation of biopsy practice and testing and therefore the costs of testing per patient treated with trastuzumab; and
- the overall increase in the cost of testing to support trastuzumab.

The PBAC noted the clinical context is treatment of a type of cancer which is uncommon, but with a rising incidence, which affects patients at about 60 years of age, which has a poor prognosis and which does not have many effective therapy options. The PBAC also noted that the intent of the proposed risk-share arrangement was proposed.

As accepted by the applicant, the PBAC reaffirmed its previous proposal to exclude patients with stage III disease from any recommended restriction, mainly because only 3.4% of patients had stage III in the key randomised trial (ToGA). The current standard treatment of stage III is chemo radiotherapy with or without surgery or chemotherapy alone if the patient is unfit. Listing for stage III would support the use of trastuzumab with radiation in some patients for whom the profile of benefits and harms is unknown. Any future reconsideration of trastuzumab in the treatment of stage III disease could be based on trials which are currently recruiting. A consequence of this would be that the estimated financial implications should be reduced by 15.6%, which represents the proportion of the identified Australian population with Stage III disease.

The PBAC considered that prolonged use of trastuzumab beyond disease progression would be likely. This use is not justified in terms of cost-effectiveness by the ToGA trial, which assessed trastuzumab concomitantly with six cycles of cisplatin with fluorouracil followed by monotherapy with trastuzumab until disease progression. In practice trastuzumab will be likely continued beyond disease progression as a monotherapy backbone with concomitant second and third line chemotherapy added intermittently. The PBAC proposed that this use, of unknown cost-effectiveness, would need to be addressed by a risk share arrangement.

The PBAC reaffirmed its previous position that any PBS restriction would also need to specify a suitable definition of HER2 positive status, consistent with PBAC acceptance of a sufficient incremental treatment effect of adding trastuzumab, and MSAC advice on the

adequacy of HER2 testing strategies to accurately identify patients according to this definition. The PBAC noted that HER2 status in the ToGA trial was assessed under optimal circumstances, with a single laboratory expert centre assessing all samples using FISH and IHC on predominately resection specimens (80%). In contrast, in Australia, HER2 status would be determined by multiple laboratories using biopsy specimens. The PBAC agreed that, in this disease, pre-screening of diagnostic samples with IHC is needed (unlike in breast cancer) to locate those parts of a specimen which would be most suitable for further investigation by FISH, CISH or SISH.

The PBAC recalled that the prognostic impact of HER2 positive status on prognosis and on predicting variation in the treatment effect of trastuzumab is less certain in gastric/gastro-oesophageal cancer than in breast cancer. It noted there is no further information to address these uncertainties in the resubmission, and considered that they were unlikely to be resolved in the near future.

Similarly, the PBAC considered that no convincing information had been provided to address its previous concerns over the use of triplet chemotherapy costs in the modelling whilst projecting doublet chemotherapy outcomes from the ToGA trial. This approach favours the sponsor by including a clearly cost-ineffective third chemotherapy drug as a source of cost offsets for trastuzumab. The basis for this approach was a survey which reported that triplet is the preferred treatment for 80% of patients. PBAC did not accept the costs of triplet therapy as a valid measure of its value given that the clinicians had clearly indicated that doublet therapy was equivalent to triplet therapy and the latter was associated with additional side effects and costs without additional benefit.

The PBAC noted that the magnitude of the clinical benefit is small: a statistically significant but clinically borderline increase in the primary outcome of overall survival in the intention-to-treat analysis of the ToGA trial (a gain of 2.7 months from a median of 11.1 months without trastuzumab to a median of 13.8 months with trastuzumab). The progression-free survival increased by 1.2 months from a median of 5.5 months without trastuzumab to a median 6.7 months with trastuzumab. In July 2011, the PBAC accepted these data as convincing evidence of trastuzumab's clinical effectiveness in HER2 positive patients as defined for this trial, noting also that the open-label nature of the trial leaves some concern about a risk of bias in favour of adding trastuzumab. Further, in July 2011, the PBAC noted that no incremental effect was detected on quality of life, but patients in the trastuzumab arm of the trial experienced 22% more adverse events than patients in the control arm of the trial.

The PBAC considered that the submission's estimate in the range of $75,000 - $105,000 per extra quality-adjusted life-year gained based on the intention-to-treat population was unacceptably high and increased by approximately $22,000 when adjusted for the pre-PBAC response to address five concerns identified in the evaluation. Accepting more favourable incremental ratios would require an acceptance that the treatment effect estimates generated post hoc could be relied upon, and the corresponding HER2 testing strategy could be implemented in regular Australian practice. These ratios underestimated the costs of testing per treated person (as per the supplementary table in the Joint ESC report), the extent of retesting (likely greater than the 10% assumed), the likely extent of false test results under less optimal circumstances than for the ToGA trial, and also omitted the costs of multiple gated acquisition scans associated with trastuzumab.

The PBAC noted the estimated financial implications were less than $4 million per year to the Government.

The PBAC also requested a response from the applicant on the additions to its proposed risk-share arrangement. This should include a revised set of economic evaluations (across the MSAC-supported scenarios and including the ToGA ITT scenario) for independent verification and should be presented when the other matters identified above as the basis for the deferral are provided to the Committee.

The PBAC acknowledged and noted the consumer comments on this item.

***Recommendation***:
**Defer**

## 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

Roche is assessing the next steps in the development of a response to any requests for further information.