**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:** July 2011

## 1. Purpose of Application

The submission sought to extend the current Section 100 Authority required listing to include treatment of human epidermal growth factor receptor 2 (HER2) positive advanced (equivalent to stage III or IV) adenocarcinoma of the stomach or gastro-oesophageal junction (referred to as advanced gastric cancer), in patients who have not received prior anti-cancer treatment for advanced disease, in combination with cisplatin and either capecitabine or 5-fluorouracil (5-FU), with a WHO performance status of 2 or less.

The submission also requested listing on the Intravenous Chemotherapy Supply Program.

## 2. Background

This drug had not previously been considered by the PBAC for this indication.

Trastuzumab for the treatment of HER2 positive early breast cancer commencing concurrently with adjuvant chemotherapy following surgery has been available on the PBS since 1 December 2006.

## 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:
  a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease;
  b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or
  c) 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 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.

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.

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 a 3 monthly intervals during treatment.

The submission proposed the following three options for testing HER2 positivity for inclusion in the restriction to determine eligibility for PBS-subsidised treatment with trastuzumab:

Scenario 1

Immunohistochemical (IHC) evidence of HER2 over expression 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 2:

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

Scenario 3:

Immunohistochemical (IHC) evidence of HER2 over expression as described by a 3+ IHC score.

The PBAC considered that the interpretation of the entire submission relied heavily on how HER2 positivity/over expression is defined, in terms of both test methodologies used and test algorithm applied.

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

## 5. Clinical Place for the Proposed Therapy

Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related deaths worldwide. Most patients present with inoperable advanced or metastatic disease requiring palliative treatment. Five-year survival for advanced or metastatic gastric cancer is around 5-10%, with median overall survival (OS) being less than 1 year.

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 submission nominated cisplatin plus a fluoropyrimidine (CF), where the fluoropyrimidine is 5-fluorouaracil or capecitabine, as the comparator for trastuzumab + cisplatin + a fluoropyrimidine (HCF). This was the comparator treatment arm in the key trastuzumab trial (ToGA) presented in the submission. This is not the current standard of care in clinical practice, which is triplet therapy consisting of epirubicin, cisplatin and fluoropyrimidine (ECF) and was the comparator presented in the submission's estimates of financial implications, rather than the CF doublet chemotherapy. The PBAC considered the appropriate comparator is triplet therapy (ECF or ECX).

### Comparator for HER2 testing

No evidence was presented comparing HCF versus ECF in the situation where there is no testing for the biomarker. Thus a comparative assessment of the impact of testing versus no testing and the comparative treatment effect of adding trastuzumab to CF in the no testing setting was not possible. It was therefore unclear whether trastuzumab resulted in an overall survival (OS) benefit irrespective of targeting according to biomarker status.

No evidence was presented of ECF (or CF) use in a HER2 negative population. Therefore determining whether HER2 status is an independent prognostic modifier, from a comparison between the biomarker positive and biomarker negative control treatment arms, was not possible from the evidence presented.

## 7. Clinical Trials

The submission presented one randomised open-label trial (ToGA), comparing trastuzumab (8 mg/kg 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)) versus 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 (OS).

The published trial presented in the submission is shown in the table below.

| Trial ID / First author | Protocol title/ Publication title | Publication citation |
|---|---|---|
| ToGA<br>BO18255 | Clinical Study Report – BO18255: An open label randomised multicentre Phase III study of trastuzumab in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone as first-line therapy in patients with HER2 positive advanced gastric cancer. Report No. 1032349, August 2009 | August 2009 |
| Bang et al. | Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive | *The Lancet* 2010; 376 |

| | | |
|---|---|---|
| | advanced gastric or gastro oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. | (9742): 687-697 |

HER2=Human epidermal growth factor receptor 2.

## 8. Results of Trials

The OS results are summarised below.

**Scenario 1 = IHC3+, or ISH+ irrespective of IHC status (Intention-to-treat (ITT) population of ToGA trial):**

**Summary of OS (Scenario 1, ToGA ITT population)**

| Overall survival | HCF (N=294) | CF (N=290) |
|---|---|---|
| Patients with event (Death from any cause) | 167 (56.8%) | 182 (62.8%) |
| Patients without events* | 127 (43.2%) | 108 (37.2%) |
| Time to event (months)<br>Median (95% CI) # | 13.8 (12, 16) | 11.1 (10, 13) |
| p-value (log-rank test) | 0.0046 | |
| Hazard ratio (95% CI) | 0.74 (0.60, 0.91) | |

* Censored; # Kaplan-Meier estimate; CI=confidence interval; CF=cisplatin/fluoropyrimidine; HCF=trastuzumab/cisplatin/fluoropyrimidine; ITT=intent-to-treat

The observed hazard ratio (non-stratified analysis) indicated a 26% reduction in the risk of death over the trial duration which was statistically significant (HR: 0.74; 95% CI: 0.60, 0.91; p=0.0046) for patients in the HCF arm, compared with patients in the CF arm. The statistically significant increase in the primary outcome of OS 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) was accepted as convincing evidence of trastuzumab's clinical effectiveness in HER2 positive patients as defined for this trial. However the PBAC also noted that the median OS in the doublet control arm (CF alone) is numerically greater than the results of four epirubicin studies with similar sample sizes, which does not support the initial biological arguments that HER2 positive status would identify a group of patients with a worse prognosis. The PBAC also questioned the clinical importance of the extent of OS gain, particularly as the comparison was not against triplet chemotherapy.

The results for the pre-specified HER2 subgroups are summarised below.

**OS by pre-specified HER2 subgroups**

| HER2 Result (ToGA)[§] | HCF | | | CF | | | HR (95%CI) |
|---|---|---|---|---|---|---|---|
| | N | Events (death) | Median time to death (months) | N | Events (death) | Median time to death (months) | |
| IHC0/FISH+ | 23 | 15 | 10.6 | 38 | 24 | 7.2 | 0.92 (0.48, 1.76) |
| IHC1+/FISH+ | 38 | 28 | 8.7 | 32 | 21 | 10.2 | 1.24 (0.70, 2.20) |
| IHC2+/FISH+ | 80 | 51 | 12.3 | 79 | 53 | 10.8 | 0.75 (0.51, 1.11) |
| **IHC3+/FISH+** | **131** | **61** | **17.9** | **125** | **76** | **12.3** | **0.58 (0.41, 0.81)** |
| IHC3+/FISH- | 9 | 5 | 17.5 | 6 | 4 | 17.7 | 0.83 (0.20, 3.38) |

**Bolded=statistically significant**

[§]Results not presented for IHC no result/FISH+ and IHC3+/FISH no result

CF=cisplatin/fluoropyrimidine; CI=confidence interval; FISH=fluorescence *in situ* hybridisation; HCF=trastuzumab/cisplatin/fluoropyrimidine; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry.

The results of testing for interaction as a likelihood ratio test between treatment and "HER2 Result" as a covariate (amongst a total of 15 separate covariate tests in each case) were not statistically significant. The PBAC noted that this negative overall test for interaction between treatment effect of adding trastuzumab to CF with varying HER2 expression in FISH+ patients cast doubt on the interpretability of the post hoc subgroup analyses presented in the submission.

**Scenario 2 = IHC2+ and ISH+, or IHC3+ irrespective of ISH status (base case, 'high' HER2, post hoc subgroup):**

The submission claimed that there was little contribution to the overall increase in efficacy from the subgroups with low expression of HER2 protein (IHC0/FISH+: HR=0.92; 95% CI: 0.48, 1.76; IHC1+/FISH+: HR=1.24; 95% CI: 0.70, 2.20) and that the main effect was derived in the subgroups of patients expressing high levels of HER2 protein (IHC2+/FISH+: HR=0.75; 95% CI: 0.51, 1.11; IHC3+/FISH+: HR=0.58; 95% CI: 0.41, 0.81). This led to a post hoc categorisation and analysis of two subgroups in the study report: "high HER2" and "low HER2" expressing subgroups. The addition of trastuzumab to chemotherapy in the 'high' HER2 expressing group (Scenario 2) resulted in a median overall survival of 16.0 months for HCF versus 11.8 months for CF: non-stratified HR=0.65 (95% CI: 0.51, 0.83) with a statistically significant interaction test (p=0.036) of the treatment effect and the HER2 category for OS between the groups.

The choice of the 'high' HER2 expressing population as the base case was determined from post hoc subgroup analyses. The OS between treatment arms, in the IHC3+/FISH- subgroup (HR=0.83; 95% CI: 0.20, 3.38) and the IHC2+/FISH+ subgroup (HR: 0.75; 95% CI: 0.51, 1.11) was not statistically significant.

**Scenario 3 = IHC3+ irrespective of ISH status (*post hoc* subgroup):**
The submission stated that the OS benefit in this group is greater than in the 'high' HER2 expressing subgroup (Scenario 2). The result for this latter group was mostly driven by the IHC3+/FISH+ population which made up the majority of the "IHC3+ regardless of FISH status" population. There were no baseline data provided in the submission or Clinical Study Report to assess the comparability between treatment groups for this subgroup of patients.

Overall, the OS results of the post hoc analyses presented as Scenarios 2 and 3 were interpreted cautiously by the PBAC as they were not pre-specified.

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

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 safety profile of trastuzumab was similar to that for other indications, for example breast cancer. The ToGA trial population was a low-risk population for toxicity, obtained by stringent exclusion criteria particularly for cardiovascular risks associated with trastuzumab (others include cancer-related, haematological, biochemical, physiological, and general exclusion criteria). These trastuzumab-related exclusion criteria resulted in a trend towards the null in terms of the drug's comparative safety. In clinical practice, such stringent exclusion criteria are unlikely to be applied to a similar extent. Thus the observed trastuzumab-related adverse events from the ToGA trial would have likely been an underestimate of adverse events in clinical practice.

Cardiac events from the ToGA trial: 9 (3.1%) patients in the CF arm experienced ≥1 cardiac Grade ≥3 AE compared with 4 (1.4%) patients in the HCF arm. The number of events was too small in either treatment arm for any meaningful comparison.

The Periodic Safety Update Report did not indicate any additional new safety signals to those already recognised to be associated with trastuzumab.

## 9. Clinical Claim

The submission described trastuzumab, when used in combination with CF as superior in terms of comparative effectiveness and no worse in terms of comparative safety over CF alone.

Based on the supporting data for comparative effectiveness, this description was reasonable for the ITT population (Scenario 1) and the pre-specified subgroup IHC3+/FISH+. Post hoc analyses for the 'high' HER2 expressing subgroup (Scenario 2 base case) and the IHC3+ regardless of FISH status subgroup (Scenario 3), also supported this contention. However, the comparative effectiveness of HCF versus the currently accepted comparator in clinical practice (ECF), in HER2 tested or non-tested advanced gastric cancer patients, remained unclear.

Based on the supporting data for comparative safety, the claim in the submission with respect to comparative safety was not reasonable. Overall, there are some additional adverse events in the HCF arm compared to the CF arm (patients in the HCF arm experienced about 22% more adverse events than patients in the CF arm) from the ToGA trial safety population. It was acknowledged that current practice is aimed at avoiding cardiovascular events by the application of cardiovascular eligibility criteria and prospective cardiac monitoring for trastuzumab. This would be important as the ToGA trial population was a low-risk population for toxicity, obtained by stringent exclusion criteria. A higher trastuzumab-related toxicity profile, compared to the ToGA trial, would be anticipated in clinical practice.

## 10. Economic Analysis

A stepped economic evaluation was presented. The economic model sought to compare the proposed scenario in which both HER2 testing and trastuzumab are subsidised against the current scenario where neither HER2 testing nor trastuzumab are subsidised.

Based on modelled evaluation costs and quality adjusted life years (QALYs) gained over a 5-year time horizon, the incremental cost per extra QALY gained for Scenario 1 was in the range of $75,000 - $105,000.

Based on modelled evaluation costs and QALYs gained over a 5-year time horizon, the incremental cost per extra QALY gained for Scenarios 2 and 3 was in the range of $45,000 - $75,000.

## 11. Estimated PBS Usage and Financial Implications

The submission estimated total net costs to the PBS (including patient co-payment) to be less than $10 million in each of Scenarios 1, 2 and 3 in year 5.

## 12. Recommendation and Reasons

The PBAC decided not to recommend trastuzumab for gastric cancer as proposed on the basis of unacceptably high and uncertain incremental cost-effectiveness ratios. In reaching this conclusion, all three scenarios proposed in the submission were considered and rejected.

The PBAC accepted ESC advice that the interpretation of the entire submission relies heavily on how HER2 positivity/over expression is defined, in terms of both test methodologies used and test algorithm applied.

The PBAC considered that the determination of HER2 positive status using various in situ hybridisation (ISH) tests and/or immunohistochemistry (IHC) tests is less certain in gastric cancer than in breast cancer. HER2 status in the key randomised trial (ToGA) was assessed under optimal circumstances, with a single laboratory assessing all samples using a battery of tests which were combined to influence the overall conclusion. For example, IHC testing helped locate those parts of a specimen which would be most suitable for further investigation by fluorescence ISH (FISH). Alternative testing strategies (such as IHC alone or FISH alone) and examination across multiple laboratories (especially if the assessment of IHC is in a different laboratory than the assessment of FISH) are both likely to produce greater discordance about which samples are FISH positive or IHC3+. Further, evidence from the Australian GaTHER study demonstrates the well-described variability in HER2 status determinations across laboratories and across the three current ISH test options and particularly across the current IHC test options. Scoring systems to determine test results also vary across breast cancer and gastric cancer and across laboratories; for example the ToGA trial relied on a HER2:CEP17 ratio >2.0 in concluding FISH positivity, whereas in breast cancer it is now widely accepted that >2.2 is FISH positive and ratios between 1.8 and 2.2 are equivocal. Similarly, use of absolute HER2 copy number, use of single and/or dual probes and assessment of surface and invasive components of the cancer may also vary between laboratories. Greater variability of HER2 positivity is also expected with specimens from endoscopy biopsies rather than resections (and more ToGA participants with biopsy specimens were diagnosed HER2 positive than were participants with resection specimens) and with specimens from metastases rather than the original tumour. In the event that trastuzumab is to be reconsidered, the PBAC accepted advice to have the Medical Services Advisory Committee's (MSAC) input on the comparative analytical performance in normal Australian laboratory conditions. Against this evidentiary standard, examining the various HER2 positive definitions, HER2 tests and testing strategies would be informative.

The PBAC further considered that the prognostic impact of HER2 positive status on prognosis and on predicting variation in the treatment effect of trastuzumab is also less certain in gastric cancer than in breast cancer. There is emerging evidence, including from the ToGA trial, that being HER2 positive may confer a more favourable prognosis in gastric cancer than being HER2 negative. If so, the biological basis for trastuzumab's pharmacological effect in inhibiting HER2 signalling is not as compelling as it is in breast cancer. The ToGA trial assessed the treatment effect of trastuzumab in patients who were HER2 positive defined as being FISH positive and/or IHC3 positive; the comparative treatment effect of trastuzumab in patients who are FISH negative and IHC0, IHC1 or IHC2 has not been investigated.

In addition, the PBAC considered that there is less biological plausibility in the claimed linkage between HER2 positive status and the incremental effect of trastuzumab arising from the greater amount of discordance across IHC and FISH results in gastric cancer, where 131 (24%) of FISH positive patients in the ToGA trial were IHC0 or IHC1+ and a further 159 (29%) of FISH positive patients were IHC2+. FISH assesses gene amplification in the cell nucleus and IHC assesses protein expression on the cell surface, and closer concordance between these results would have given greater support to the underlying biological rationale and greater confidence in the post hoc subgroup analyses relied on in the submission.

The PBAC noted that, with only 3% of the ToGA population having locally advanced (Stage III) disease, any reconsideration of trastuzumab in gastric cancer should be limited to those with metastatic (Stage IV) disease. For similar reasons with reference to the ToGA trial, trastuzumab should not be continued after disease progression. 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 considered that the appropriate comparator is triplet chemotherapy, such as epirubicin with cisplatin and either 5-fluorouracil or capecitabine (ECF or ECX) rather than doublet therapy such as cisplatin and either 5-fluorouracil or capecitabine (CF), and that triplet chemotherapy has been established to be more effective than doublet chemotherapy, albeit on comparatively weak evidence. As the evidence from the ToGA trial compared the addition of trastuzumab to CF against CF alone, this was a source of uncertainty in the submission.

The statistically significant 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) was accepted as convincing evidence of trastuzumab's clinical effectiveness in HER2 positive patients as defined for this trial. However the PBAC also noted that the median overall survival in the doublet control arm (CF alone) is numerically greater than the results of four epirubicin studies with similar sample sizes, which does not support the initial biological arguments that HER2 positive status would identify a group of patients with a worse prognosis. The PBAC also questioned the clinical importance of the extent of overall survival gain, particularly as the comparison was not against triplet chemotherapy. 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 economic model sought to compare the proposed scenario in which both HER2 testing and trastuzumab are subsidised against the current scenario where neither HER2 testing nor trastuzumab are subsidised.

The economic model for the intention-to-treat population (Scenario 1) estimated a base case discounted incremental cost in the range of $75,000 - $105,000 per extra discounted quality-adjusted life-year gained, which the PBAC considered to be unacceptably high and uncertain. Uncertainties highlighted in the sensitivity analyses included the effectiveness of current therapy in the comparator scenario and the HER2 negative patients in the proposed scenario. In both these cases, the approach taken in the submission was favourable to trastuzumab. This is of particular concern given doubts about whether being HER2 positive confers a poorer prognosis in gastric cancer. Other important uncertainties include the comparison against less effective doublet chemotherapy and the lack of adjustment for less optimal HER2 testing in Australia. In both these cases, the approach taken in the submission was also favourable to trastuzumab.

The PBAC also considered two alternative scenarios based on post hoc subgroups proposed in the submission. The reliability of these scenarios was considered to be insufficiently justified given the negative result of the pre-specified test for interaction between the treatment effect of trastuzumab and five pre-specified HER2 subgroups: four being defined by patients being FISH positive and in one of the four different IHC states, and the other being defined by patients being FISH negative and IHC3+. The post hoc subgroups were defined differently: IHC3+ irrespective of FISH status OR IHC2+ and FISH positive (Scenario 2) or IHC3+ irrespective of FISH status (Scenario 3). The PBAC noted that the median overall survival in the control arm tended to increase numerically as the definition of HER2 positivity for each subgroup was increased with reference to their IHC state, which again does not support the initial biological arguments that HER2 positive status would identify a group of patients with a worse prognosis. Both post hoc subgroup scenarios were associated with numerically larger gains in overall survival and numerically more favourable incremental cost-effectiveness ratios, with Scenario 3 numerically more favourable than Scenario 2. The PBAC considered these ratios to still be unacceptably high and even more uncertain than the base case from the overall analysis.

The PBAC considered that MSAC input would be informative on: (a) the analytical performance and effective analytical performance of IHC and ISH and various strategies of combining these tests; (b) the HER2 copy number data from the ToGA trial; (c) clarifying the prognostic significance of HER2 status in gastric cancer; (d) an implementation strategy for HER2 testing of gastric cancer in Australia which marries what is practical with the data available from ToGA; (e) a more detailed assessment of the GaTHER study, with particular reference to IHC variability which is not included in the submission and with reference to concordance in terms of who would and would not be eligible for trastuzumab according to different definitions of HER2 positive rather than reference to Kappa statistics.

***Recommendation***:
**Reject**

## 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

The sponsor had no further comment.