**PUBLIC SUMMARY DOCUMENT**

**Product:** Lapatinib ditosylate monohydrate, tablet, 250mg (base), Tykerb®

**Sponsor:** GlaxoSmithKline Australia Pty Ltd

**Date of PBAC Consideration:** July 2007

## 1. Purpose of Application

The submission sought a section 100 (Highly Specialised Drug) listing for lapatinib for use in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and who have received prior therapy including trastuzumab.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

## 2. Background

This drug had not previously been considered by the PBAC.

## 3. Registration Status

Lapatinib was TGA registered on 28 June 2007 for the treatment, in combination with capecitabine, of patients with advanced/metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and whose tumours have progressed after treatment with an anthracycline, a taxane and trastuzumab.

## 4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug) Private hospital authority required

A revised use in combination with capecitabine for the treatment of patients with advanced /metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and whose tumours have progressed after treatment with an anthracycline, a taxane and trastuzumab.

The PBAC noted that the submission sought to list lapatinib for second line use in patients with HER2 positive breast cancer who had failed trastuzumab in the metastatic setting, but that the restriction proposed did not so limit its use and would allow lapatinib to be used first line in the metastatic setting after any use of trastuzumab for early breast cancer.

The PBAC considered that the restriction should be modified to specify that the patient had either failed trastuzumab in the metastatic setting or had experienced disease progression while receiving, or shortly after completing adjuvant trastuzumab treatment. The restriction should also specify that lapatinib must not be used in combination with trastuzumab, or with any chemotherapy other than capecitabine and that evidence of HER2 status consistent with the listing for adjuvant trastuzumab must be supplied to Medicare Australia prior to authority approval. A continuation rule may also need to be developed. The Committee agreed that a Section 85 listing is appropriate and noted that the sponsor is willing to negotiate on the restriction wording.

## 5. Clinical Place for the Proposed Therapy

In recent years, the advent of targeted therapies has offered new treatment options for breast cancer patients. In Australia, trastuzumab has become the standard treatment for women with HER2 (ErbB2) overexpressing breast cancer in the metastatic and early breast cancer setting. Overexpression of HER2 has been associated with poor prognosis and reduced overall survival.

While a proportion of patients diagnosed with HER2 (ErbB2) overexpressing breast cancer who take trastuzumab will no longer go on to develop more advanced forms of the disease, there continues to be a clinical need for additional treatment options for those patients whose disease progresses to advanced or metastatic breast cancer.

Lapatinib is a small molecule reversible tyrosine kinase inhibitor that targets both the epidermal growth factor receptor (EGFR) and the HER2 receptor. It will provide a treatment option for patients who need an additional treatment following trastuzumab.

## 6. Comparator

The submission nominated both capecitabine monotherapy and trastuzumab plus capecitabine as comparators.

The PBAC agreed that capecitabine monotherapy was an appropriate comparator, but did not agree that capecitabine plus trastuzumab was also an appropriate comparator.

## 7. Clinical Trials

The submission presented one randomised trial comparing lapatinib (1250 mg/day) continuously plus capecitabine (2000 mg/m$^2$/day on days 1 – 14 of every 21 days) with capecitabine monotherapy (2500 mg/m$^2$/day on days 1 – 14 of every 21 days) in patients who have failed treatment with trastuzumab in the metastatic setting.

This trial had been published at the time of submission, as follows:

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **EGF100151** Geyer CE et al, 2006 | Lapatinib plus capecitabine for HER2-positive advanced breast cancer. | N Engl J Med. 2006 Dec 28;355(26):2733-2743 |

The submission does not provide any evidence of the comparative efficacy and safety of lapatinib plus capecitabine versus trastuzumab plus capecitabine.

## 8. Results of Trials

The population recruited to trial EGF100151 were eligible for treatment with lapatinib if they had HER2 positive locally advanced or metastatic breast cancer that had progressed after treatment with regimes that included an anthracycline, a taxane and trastuzumab. Trastuzumab administered in the adjuvant setting was not exclusionary, but, for eligibility, trastuzumab must also have been administered in the locally advanced or metastatic setting.

An independent review committee for study EGF100151 was responsible for reviewing the time to progression (TTP) primary outcome measure data. Assessment intervals for TTP measurements were pre-specified in the study protocol, and assessors were blinded to treatment arm and subject outcome.

The published results of the trial are summarised below.

**Time To Progression (TTP) evaluated by independent review in Trial EGF100151 (according to analysis performed after discontinuation of study) as reported in submission**

| | Lapatinib + capecitabine N=198 n (%) | Capecitabine monotherapy N=201 n (%) | Difference |
|---|---|---|---|
| **Progression and death (median follow-up not specified), n (%)** Progressed or died due to breast cancer | 82 (41) | 102 (51) | -10% |
| **Cumulative incidence estimate of TTP, in weeks** Median | 27.1 | 18.6 | 8.5 |
| **Hazard ratio** Estimate, (95% CI) Log-rank p-value | **0.57 (0.43, 0.77) 0.00013** | | |

**Overall survival (OS) in Trial EGF100151 (according to analysis performed after discontinuation of study) as reported in submission**

| | Lapatinib + capecitabine N=198 n(%) | Capecitabine monotherapy N=201 n(%) |
|---|---|---|
| **Kaplan-Meier estimate of OS in weeks** Median (95% CI) | 67.7 (58.9, 91.6) | 66.6 (49.1, 75.0) |
| **Hazard ratio** Estimate (95% CI) Log-rank p-value | 0.78 (0.55, 1.12) 0.177 | |

Although the surrogate outcome of time to progression reached statistical significance, there was no statistically significant difference in overall survival between the lapatinib+capecitabine and capecitabine alone arms.

The study was terminated early by the independent monitoring board due to the positive findings in time to progression for the lapatinib+capecitabine treated patients. All subjects were provided access to treatment with lapatinib following termination of the study. The early termination of the study reduces the likelihood of detecting a significant difference in overall survival.

The most common adverse events reported in trial EGF100151, regardless of duration of exposure, were diarrhoea, palmar-plantar erythrodysaesthesia (PPE), nausea (distinct from PPE), rash and fatigue. Most adverse events were grade 1 or 2, the incidence of serious adverse events (4%) and discontinuations due to adverse events (12-13%) were similar in the lapatinib plus capecitabine and capecitabine alone treatment groups. Statistically significant higher incidences of diarrhoea, rash and dyspepsia were reported in the lapatinib plus capecitabine group compared with the capecitabine monotherapy group.

Left ventricular ejection fraction (LVEF) was reduced in 6 women in the lapatinib plus capecitabine versus 1 in the capecitabine monotherapy group.

*For PBAC's comments on these results, see Recommendation and Reasons.*

## 9. Clinical Claim

The submission to PBAC claimed that lapatinib plus capecitabine has significant advantages in effectiveness over capecitabine and no greater toxicity.

*For PBAC view of this claim, see Recommendation and Reasons.*

## 10. Economic Analysis

The submission presented a stepped economic evaluation. The choice of a cost-utility approach was considered valid. However, the PBAC considered the inclusion of trastuzumab plus capecitabine as a main comparator inappropriate. The resources included were drug costs and specialist visits.

The incremental discounted costs per additional life year (LYG) or quality adjusted life year gained (QALY) for lapatinib plus capecitabine versus capecitabine alone both fell in the range $45,000 - $75,000 when the cost of continuing trastuzumab (even after progression had occurred while on it) was taken into account. When the cost of continuing trastuzumab was excluded, the costs per LYG or QALY fell in the range $110- $200,000.

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

## 11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 1 of listing the financial cost/year to the PBS would be in the range $10 – $30 million.

## 12. Recommendation and Reasons

The Committee agreed that there is some evidence that lapatinib plus capecitabine improves survival compared to capecitabine alone in patients with HER2 positive metastatic disease which has progressed despite treatment with trastuzumab, but that the full extent of this survival benefit is not known and although it is trending towards a significant result, it is not statistically significant.

The PBAC also concluded that lapatinib plus capecitabine is associated with a higher incidence of diarrhoea, rash and dyspepsia compared to capecitabine alone

The PBAC agreed that capecitabine monotherapy was an appropriate comparator, but did not agree that capecitabine plus trastuzumab was also an appropriate comparator. When used in combination with chemotherapy in metastatic breast cancer, trastuzumab is most commonly combined with a taxane, vinorelbine or platinum. Additionally, statistics from the Herceptin Program (the non-PBS trastuzumab metastatic disease program) indicate that approximately half of patients in the advanced setting are treated with trastuzumab as monotherapy.

The Committee further considered that the use of trastuzumab as a cost offset in the stepped economic evaluation rests on inadequately supported assumptions and as the cost-effectiveness of continuing trastuzumab in patients whose metastatic disease has progressed despite treatment with trastuzumab is unknown an analysis including such continuation does not provide an appropriate basis for determining the cost-effectiveness of lapatinib.

The PBAC thus considered that the most reliable current estimate of the cost-effectiveness of lapatinib per discounted cost per additional discounted life-year gained (LYG) or per

discounted quality adjusted life year (QALY) over 5 years fell in the range $110,000 - $200,000. These were considered unacceptably high by the Committee.

The PBAC therefore rejected the submission on the basis of an unacceptable cost effectiveness ratio.

***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 disagrees with the conclusions of the Committee and is disappointed with the decision. All options will continue to be explored to secure funding for lapatinib, to ensure access for patients at the earliest possible opportunity.