PUBLIC SUMMARY DOCUMENT
Product: Lapatinib ditosylate, tablets, 250 mg, Tykerb®
Sponsor: GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The re-submission sought Section 85 listing on the PBS for metastatic HER2 positive breast cancer.

2. Background

The PBAC rejected a submission to list lapatinib for the treatment of metastatic HER2 positive breast cancer at its July 2007 meeting on the basis of an unacceptable incremental cost-effectiveness ratio.

At a meeting between the PBAC Chair and GlaxoSmithKline (GSK) following this rejection, GSK indicated it had new data to inform some pivotal areas of PBAC uncertainty. Specifically, GSK had conducted a systematic review of the literature and obtained further information on current clinical practice in Australia. The PBAC invited GSK to make another submission for consideration at the November 2007 meeting.

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

Authority required

Initial treatment of patients with HER2-positive metastatic breast cancer who have received prior therapy with an anthracycline and a taxane administered either concurrently or separately, except where the patient is intolerant or contra-indicated to those agents, and whose disease progresses despite treatment with trastuzumab or who meet the trastuzumab-exemption criteria (see eligibility criteria point (d) below).

1. Eligibility
   (a) patients must have documented evidence of HER-2 positive breast cancer determined by either of the following methods :
   - HER2 protein overexpression by immunohistochemistry (IHC) at the 3+ level; OR
   - HER2 gene amplification by in-situ hybridisation (ISH – fluorescent or cromogenic)

   (b) Prior therapy with anthracycline or taxane, defined as :
   - taxane containing regimen for at least 3 cycles, except where disease progression occurred while on taxane, or in cases of intolerance or contraindication.
   - anthracycline containing regimen for at least 3 cycles except where disease progression occurred while on anthracyclines, or in cases of intolerance or contraindication.

   (c) Trastuzumab treatment is defined as one of either :
   - trastuzumab administered alone or in combination with a taxane for at least 6 weeks of standard doses in the metastatic setting; OR

   (d) Trastuzumab exemption criteria are defined as:
   - early recurrence of disease within 12 months of completing a course of trastuzumab administered for HER2-positive early breast cancer in patients receiving adjuvant treatment following surgery; OR
   - presence of CNS metastases from breast cancer following appropriate localised therapy.

1. Notes

Metastatic breast cancer is considered present when the cancer has spread beyond the breast and axillary lymph nodes to a distant site.

Lapatinib should not be commenced or continued in patients with a left ventricular ejection fraction LVEF) of less than the lower limit of normal range or with symptomatic heart failure. Adequate cardiac function must be demonstrated by a suitable method (for example, ECHO or MUGA), prior to seeking the initial authority approval and then at regular intervals during treatment.

Patients with HER2-positive metastatic breast cancer receiving treatment with lapatinib must receive concurrent treatment with capecitabine.

Lapatinib is not PBS-subsidised when used in combination with Commonwealth-subsidised trastuzumab.

Authority applications for initial treatment must be made in writing and must include:

(a) a completed authority prescription form; and

(b) declaration that HER2 gene amplification (by immunohistochemistry and/or fluorescent in situ hybridisation (FISH) has been previously confirmed

The medical practitioner should request sufficient quantity to provide for a maximum of 3 months treatment (i.e. prescription and two repeats).

Authority required
Following completion of an initial treatment course of lapatinib, patients may continue to receive treatment provided :

i) clinical benefit is continuing to be derived from treatment with lapatinib at the time of the request; AND
ii) they are not currently receiving Commonwealth subsidised treatment of trastuzumab.

1. Definition of continuing clinical benefit

i) No significant increase in the size of measurable lesions; AND
ii) No new lesions since commencement of treatment; AND
iii) No significant evidence of clinical deterioration.

2. Notes

Metastatic breast cancer is considered present when the cancer has spread beyond the breast and axillary lymph nodes to a distant site.
Lapatinib should not be commenced or continued in patients with a left ventricular ejection fraction LVEF) of less than the lower limit of normal range or with symptomatic heart failure. Adequate cardiac function must be demonstrated by a suitable method (for example, ECHO or MUGA), prior to seeking the initial authority approval and then at regular intervals during treatment.
Patients with HER2-positive metastatic breast cancer receiving treatment with lapatinib must receive concurrent treatment with capecitabine. .

The PBAC considered that the revised proposed restriction addresses most of its previous concerns, although it was considered inappropriate to allow use on the basis of an immunochemistry (IHC) result as this would be inconsistent with the current PBS listing for trastuzumab in the adjuvant setting. Some further refining of the restriction may be appropriate in the event of a listing recommendation and could be undertaken in consultation with relevant stakeholders.

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 resubmission proposed a mixed comparator of five different agents weighted by their usage as identified in an Australian Oncology Monitor (AOM) data sub-set of 51 patients, viz: capecitabine monotherapy, trastuzumab monotherapy, trastuzumab + vinorelbine, trastuzumab + capecitabine, trastuzumab + taxane, gemicitabine + taxane. The resubmission although recognizing that the data set is relatively small, claimed that the data from the AOM database is representative of the Australian population as the total population eligible for lapatinib treatment is in the order of 350-550 patients per year.

For PBAC had significant concerns with this approach, see Recommendation and Reasons.

7. Clinical Trials

The submission presented data in three areas: the efficacy of lapatinib for CNS metastases; the overall efficacy of lapatinib; and the efficacy of the nominated comparator drugs, as follows:

CNS Metastases

The submission presented an updated *ad hoc* analysis from the EGF100151 trial, the same trial as included in the July 2007 submission.

This trial has been published 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

Efficacy Update of pivotal trial EGF100151

The submission presented an updated survival analysis for study EGF100151.

Systematic Review

The submission presented a systematic review of the literature for direct randomised trials of lapatinib and any of the components of the proposed main comparator, in patients with metastatic breast cancer, with disease progression.

Trials (and associated reports) presented in the submission

Trial ID	Description	Reports
EGF100151/ Geyer	A phase III, randomised, open-label, multicentre study comparing Lapatinib and capecitabine (Xeloda) versus capecitabine in women with refractory advanced or metastatic breast cancer.	N Engl J Med. 2006 Dec 28;355(26):2733-2743.
Bartsch et al 2007	A prospective, non-randomised, open-label, single centre study investigating the safety and efficacy of capecitabine + trastuzumab as salvage therapy in pre-treated patients with MBC after earlier trastuzumab exposure.	J Clin Oncol; 25(25): 1 – 6.
(Bartsch et al 2006)	A prospective, non-randomised, open-label, single centre study investigating the safety and efficacy of trastuzumab treatment after the failure of at least one earlier trastuzumab containing therapy regimen.	BMC Cancer; 6: 63 - 68
(Furukawa et al 2006)	Retrospective cohort study examining the safety and efficacy of combined trastuzumab and paclitaxel in patients with HER2 overexpressing MBC.	Breast Cancer; 13: 329 - 333
(Montemurro et al 2006)	Multicentre, retrospective cohort study examining the patterns of treatment and clinical outcome in patients with HER2-positive MBC.	The Oncologist; 11: 318 - 324
(Garcia-Saenz et al 2005)	Single-centre, retrospective study of incident cases of continued trastuzumab therapy in association with sequential chemotherapy.	Clinical Breast Cancer; 6(4): 325 - 329
(Stemmler, HJ et al 2005)	Multicentre, retrospective cohort study evaluating the impact of continuing trastuzumab-based treatment despite tumor progression on survival.	Onkologie; 25: 582 - 586
(Tripathy D et al 2004)	Randomised, active-controlled study investigating the safety and efficacy trastuzumab in patients with MBC following disease progression.	Journal of Clinical Oncology; 22(6): 1063 – 1070
(Gelmon et al 2004)	Multicentre, retrospective case review study evaluating the efficacy of trastuzumab beyond disease progression.	Clinical Breast Cancer; 5(1): 52 - 58
(Fountzilas et al 2003)	Retrospective case review study to evaluate serious and unusual side effects from prolonged administration of trastuzumab.	Clinical Breast Cancer; 4(2): 120 - 125

8. Results of Trials

CNS Metastases

The updated ad hoc analysis from the EGF100151 trial was presented in the form of a poster by Cameron et al, 2006 at the American Society of Clinical Oncology annual meeting 2007 and shows 13 women out of 201 in the monotherapy group and 4 women out of 198 in the combination-therapy group had CNS metastases and that the difference was statistically significant (p=0.045).

Two phase II trials were also presented as evidence of the use of lapatinib in the treatment of CNS metastases in women with metastatic breast cancer. Both studies were single arm studies with no comparator.

The PBAC agreed with the submission's assessment that, although lapatinib in combination with capecitabine represents a promising option for preventing the development of CNS metastases and for treating pre-existing metastases, the evidence of its efficacy in this area must be considered preliminary.

Efficacy Update of pivotal trial EGF100151
The previous submission reported an unadjusted overall survival hazard ratio of 0.78 (95% CI: 0.55 1.12) for lapatinib + capecitabine compared with capecitabine alone. The median overall survival was 67.7 weeks compared with 66.6 weeks months respectively.

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 PBAC noted that the new submission provided no additional efficacy data for the key clinical trial (EGF 100151) beyond the update provided with the pre-PBAC response previously considered. Thus the Committee's previous conclusion regarding the efficacy of lapatinib is unchanged, viz: 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 as shown by the statistically significant difference in time to progression, but the full extent of overall survival benefit is not known and although it is trending towards a significant result, it is not statistically significantly different from capecitabine monotherapy.

Systematic Review
Based on the systemic review, the submission concluded that the efficacy of lapatinib+capecitabine treatment is comparable to that reported for trastuzumab monotherapy and trastuzumab+chemotherapy in terms of time to progression and response rate based on the evidence.

The Committee acknowledged that the new submission had conducted an appropriate review of all potentially relevant information of the comparative effectiveness of lapatinib in combination with capecitabine versus other possible therapies including continuing trastuzumab in the face of disease progression. However, the Committee was not satisfied that the efficacy of continuing trastuzumab in the face of disease progression has been demonstrated. It may be entirely ineffective, or it may, although unlikely, be more effective than switching to lapatinib with capecitabine. Overall, the PBAC was somewhat less concerned with this issue than with the issue of the proportion of trastuzumab patients who continue treatment post-failure, as it was acknowledged that the submission takes a conservative approach to this uncertainty in the economic model by assuming trastuzumab continuation is at least as effective as lapatinib plus capecitabine.

Comparative toxicity
The overall safety profile of lapatinib + capecitabine, in terms of the incidence, types and intensities of adverse events, appears similar to that reported in the published studies for different trastuzumab-containing chemotherapies for patients with metastatic breast cancer.

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

For PBAC's view of this claim, see Results of Trials above

10. Economic Analysis

The submission presented a revised modelled economic analysis. The structure of the revised model was largely unchanged from that presented in the original submission with the exception of changes made to the weighting assigned to various therapies in the comparator arm. The modelled economic evaluation used the updated hazard ratio for overall survival derived from individual patient data and the extrapolation of this data for the duration of the model.

The model assumes lapatinib treatment is discontinued upon disease progression.

The submission calculated an incremental cost effectiveness ratio which was dominant (ie lapatinib treatment is more effective and less costly than the comparator) when it was assumed that, in the event lapatinib was not subsidised, 80% of all comparator patients receiving treatment with trastuzumab would continue on that treatment even after progression of disease.

The incremental cost effectiveness ratio varied widely depending upon the assumed extent of substitution of lapatinib for continued treatment with trastuzumab. This variation was particular marked around the range 50 – 80% of continuing trastuzumab use.

The assumed rate of substitution for continuing trastuzumab remained a critical issue of concern to the PBAC, *see Recommendation and Reasons.*

11. Estimated PBS Usage and Financial Implications

The submission presented revised PBS utilisation estimates for lapatinib as a dispensed price for maximum quantity over five years as a Section 85 item to be less than $10 M in year 5.

12. Recommendation and Reasons

The PBAC noted that this new submission provided data to address some of the pivotal issues which had lead to the rejection of a listing application for lapatinib previously. The submission also reviewed the available data for lapatinib in the treatment of CNS metastases from HER-2 positive breast cancer, an identified area of clinical need, as trastuzumab does not cross the blood-brain barrier. The PBAC's view of the updated clinical data is provided in the section 8 Results in this document

The Committee was not convinced that the new submission had resolved the issue of the proportion of patients who continue with trastuzumab despite progression in Australian clinical practice. This issue continues to be critical as the incremental cost-effectiveness ratio for lapatinib with capecitabine is highly sensitive to this proportion. For example, a proportion of 50% trastuzumab 'continuers' results in a cost per QALY in the range $75,000 to $105,000.

In this context, the PBAC noted that the data from the study by Pearson et al [*J Clin Oncol* 2007; 25(24): 3688-3693], which found that the patient time on treatment (median 12.5 months) was longer than the published data from the Slamon study [*N.Eng.J.Med*. 2001; 344 (11):783-792] which was the pivotal trastuzumab trial at the time of its registration (median 6.9 months). These data suggest that the original trastuzumab trial underestimated the duration of the time to progression and do not appear to support the conclusion of extensive

trastuzumab use beyond progression. In addition, more recent trials of taxane-trastuzumab combinations have also shown a time to progression from 11.7 to 13 months, which approximates the treatment duration seen in the Australian data reported by Pearson [Marty M, et al *J Clin Oncol* 2005;23(19):4265-74, Robert N et al. *J Clin Oncol* 2006;24(18):2786-92].

The PBAC was further concerned with the small sample size and potential for bias in the Australian Oncology Monitor (AOM) data set used by the submission to support a continuation proportion of 80%. The stability over time of the AOM based estimate is also a concern. This is based on a sample of 51 patients, and a sample taken at a different time point or from a different sample of oncologists might yield a different result.

The PBAC also continued to find it difficult to reconcile the assumption in the economic modelling that lapatinib will be stopped when disease progresses with the argument that trastuzumab containing regimens are continued beyond progression. This is even less convincing when the fact that lapatinib is an oral therapy which can be taken at home, whereas trastuzumab is an intravenous therapy is taken into account.

Overall the PBAC concluded that although considerable progress towards a PBS listing recommendation had been made, there continues to be insufficient data to allow the Committee to conclude that the Government will realise the savings claimed by the submission. The PBAC accepted that a proportion of patients will continue treatment with trastuzumab upon failure, however the true extent of this use remains uncertain and the incremental cost-effectiveness ratio is extremely sensitive to this proportion. The Committee considered it possible to better inform this issue with additional data from the Australian setting.

The PBAC therefore deferred this submission, noting the two additional relevant studies that the company has not had an opportunity to comment upon and its concerns with the AOM data set; to allow further investigation to accurately determine the proportion of patients who continue with trastuzumab after disease progression, and to reconsider, if appropriate, an appropriate subsidy price for lapatinib based upon the findings of this investigation. The PBAC emphasised its willingness to continue to work with the company in resolving this issue.

Following deferral of the submission at the November 2007 PBAC meeting, GSK made a price offer for lapatinib which resulted in an ICER in the range $45,000 - $75,000.

Recommendation and Reasons arising from extraordinary PBAC meeting:
The PBAC recommended the listing of lapatinib as an authority required pharmaceutical benefit for use in combination with capecitabine, for the treatment of a patient with advanced or metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and who have progressive disease despite prior therapy including trastuzumab. This recommendation was on the basis of a high, but acceptable cost effectiveness ratio.

The Committee noted that with a price reduction ex-manufacturer offered by the sponsor, and a 50% rate of substitution of trastuzumab in patients who are progressing on the drug, the incremental cost effectiveness ratio (ICER) was in the range $45,000 to $75,000 per QALY.

In view of concerns that patients might continue lapatinib oral therapy beyond progression of the disease, the PBAC recommended that a risk-share arrangement is appropriate.

The PBAC considered there were a number of issues with the restriction that needed to be resolved, such as use of prior therapies and that the restriction should be consistent with inclusion criteria for the clinical trial. In view of concerns about patients continuing treatment beyond progression, any restriction would need to state that continued supply will not be authorised after the disease has progressed on lapatinib treatment. Further, the PBAC recommended that the restriction should stipulate requirements that would enable data to be collected to monitor appropriate utilisation of lapatinib.

The restriction should also prohibit concomitant treatment with lapatinib and trastuzumab.

Recommendation
List
Restriction to be finalised

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

GSK welcomes this decision by the PBAC to recommend listing of a new treatment option for Australian patients with advanced forms of breast whose cancer has progressed despite having had other treatments.

GSK is committed to ongoing collaboration with the Pharmaceutical Evaluation Branch and clinicians to ensure the restriction provides access to lapatinib for patients in whom the PBAC has considered it is cost effective.