Final Record of Part (Item 11**) of the**
Pharmacology and Therapeutics Advisory Committee
Meeting held on 24 & 25 May 2006

11. Trastuzumab (Herceptin)

11.1. The Committee noted that it had first reviewed the application from Roche Pharmaceuticals for the listing of trastuzumab (Herceptin) for early HER-2 positive breast cancer at its February 2006 meeting, prior to Medsafe registration. The Committee had requested that further information be provided in relation to any extended benefits and risks and that the Cancer Treatments Subcommittee of PTAC (CaTSoP) review the application.

11.2. The Committee noted that CaTSoP had reviewed the application on trastuzumab in April 2006. The Committee noted that: the supplier had provided a cost-utility analysis (CUA) on the use of trastuzumab in early HER-2 positive breast cancer; PHARMAC staff had undertaken a preliminary cost-utility analysis; and that further information had become available on the efficacy and alternative dosing schedules for trastuzumab since the previous meeting, including evidence provided by the supplier.

Minutes of CaTSoP

11.3. The Committee agreed with the considerations of the April 2006 meeting of CaTSoP regarding trastuzumab for early HER-2 positive breast cancer.

Further Clinical Information

11.4. The Committee considered that the evidence provided in the supplier's addendum to the Submission for trastuzumab did not meet the requirements of their request for information in February 2006.

11.5. Members noted that there was no further information supplied on Arm Two (trastuzumab treatment for two years) of the HERA trial (whose interim results for the one-year treatment and observation-only arms were published by Piccart-Gebhart et al N Engl J Med. 2005 Oct 20; 353(16): 1659-72). The Committee considered that these data should soon be available and consideration of these results would be important in any recommendation made.

11.6. Members noted that although the supplementary appendix to the Romond et al (N Engl J Med. 2005 Oct 20; 353(16): 1673-84) paper, as posted on the NEJM website, had been provided, the full individual results of the NSABP B-31 and NCCTG N9831 trials had not been provided as requested.

11.7. Members noted that the data contained in that appendix for the disease-free survival curves showed similar and statistically significant differences in favour of concurrent trastuzumab therapy, compared to no trastuzumab therapy, in each of the B-31 and N9831 trials. Members noted an early, unpublished analysis of disease-free survival in the N9831 trial supplied in the form of MS PowerPoint slides of a conference presentation (Perez et al. NCCTG N9831: May 2005 update, presentation at the 41st American Society of Clinical Oncology conference, May 2005). Members noted that sequential trastuzumab treatment (Arm B) was not statistically superior to non-trastuzumab treatment (Arm A), but that concurrent trastuzumab treatment (Arm C) resulted in a significant improvement in disease-free survival compared with Arm B. Members considered that although these data were preliminary, they raised concerns about the optimal dosing schedule of trastuzumab treatment. Members noted that slides from an oral presentation do not provide sufficient information to make necessary decisions.

11.8. The Committee noted results for the Breast Cancer International Research Group (BCIRG) 006 study (as yet unpublished) supplied in the form of MS PowerPoint slides of a conference presentation (Slamon D., SABCS 2005). It noted that there were three treatment arms: the first containing chemotherapy only, with four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel; the second containing the same chemotherapy regimen plus one year of trastuzumab commenced concurrently with docetaxel; and the third comprising six cycles of docetaxel and carboplatin with one year of trastuzumab commenced concurrently with the chemotherapy. Members noted that there was a significant improvement in disease-free survival in the trastuzumab treated patients; however, there was no significant difference in disease-free survival between the two trastuzumab arms. There were insufficient data to evaluate overall survival.

11.9. The Committee noted the concerns raised by CaTSoP in its consideration of cardiac toxicity associated with trastuzumab. The Committee noted that a pooled data analysis provided by the supplier, including data from HERA, NSABP B-31, NCCTG N9831 and BCIRG 006 trials, indicated that cardiac effects appear to be manageable; however, the long-term impact of these cardiac effects is unknown.

11.10. The Committee noted that the rates of cardiac dysfunction appear to be lower when trastuzumab is administered sequentially, rather than concurrently, with chemotherapy. The Committee considered that trastuzumab treatment was associated with higher rates of cardiac toxicity when used with an anthracycline-containing chemotherapy regimen.

11.11. The Committee noted the results of a sub-analysis of patients with HER-2 positive breast cancer published as part of the FinHer Study (N Engl J Med. 2006 Feb 23; 354(8): 809-20). The Committee noted that this study had not been provided by the supplier.

11.12. The Committee noted that in the FinHer trial, patients were randomized to receive three cycles of either docetaxel or vinorelbine followed by three cycles of fluorouracil, epirubicin and cyclophosphamide. Patients with HER-2 positive breast cancer were further randomised to receive or not receive nine weekly infusions of trastuzumab commenced concurrently with the first cycle of chemotherapy. The Committee noted that, after a median follow-up of 36 months, trastuzumab treatment resulted in a significant improvement in disease-free survival compared with the control group (HR 0.42, p=0.01) without the cardiac toxicity associated with 12 months trastuzumab treatment as reported in other trials.

11.13. The Committee noted that the trastuzumab treatment arms of the FinHer trial were relatively small (232 of 1,010 patients) and that the trial might not have been sensitive enough to reliably detect cardiac toxicity. However, the Committee considered that, given the proposed molecular mechanisms of trastuzumab and anthracycline cardiotoxicity, the treatment sequence used in the FinHer study (i.e. trastuzumab prior to anthracycline) might have substantially reduced the risk of developing cardiac toxicity.

11.14. The Committee considered that the FinHer Study cast significant doubt over the optimal duration and timing of trastuzumab treatment. Members noted that funding trastuzumab for the proposed indication would have a high budgetary impact, which would have significant consequences for future funding of other pharmaceuticals and services. The uncertainty surrounding the optimal duration and timing of treatment represented a large risk that should be addressed before any decision is made.

General considerations

11.15. The Committee considered that it was highly unlikely that the strict entry and exit criteria in clinical trials of trastuzumab would be adhered to in clinical practice. It considered that there might be a higher rate of adverse effects associated with trastuzumab when used

in clinical practice due to the likely difficulties in accessing the required cardiac monitoring services.

11.16. The Committee considered that the true benefit of trastuzumab in primary breast cancer in relation to its costs lay in the rate of overall survival compared with the duration of treatment. The Committee noted that, at this time, these data are immature.

11.17. The Committee considered whether trastuzumab would be used to treat a patient with metastatic breast cancer, if it had already been administered to that patient in the early stages of their breast cancer. The Committee considered that it might be difficult to enforce a restriction on the use of trastuzumab to either primary or metastatic breast cancer. It considered that some physicians would wish to use trastuzumab in both stages of disease if there was a significant time between treatments. The Committee considered that re-treatment with trastuzumab would significantly increase expenditure and was not supported by trial data. The Committee noted that CaTSoP considered that patients should not be re-treated with trastuzumab should the disease recur following treatment for the primary disease.

11.18. The Committee reiterated the minute of CaTSoP who considered that, at present, both infusion and echocardiogram services are working at, or near, capacity in DHB hospitals. If trastuzumab were available for early breast cancer, the Committee considered that it may result in increased waiting times for existing cancer treatments and adversely impact on cardiology services.

Cost-Utility Analysis

11.19. The Committee reviewed the cost-utility analyses on the use of trastuzumab in the primary setting. The Committee considered that length of relative benefit from trastuzumab would need to be addressed before any further work on other factors such as management of adverse effects was undertaken, to enable an estimate regarding the cost-utility of trastuzumab to be made reliably. The Committee considered that the availability of longer-term data would inform this process.

Recommendation

11.20. The Committee concluded that, based on the interim trial results published to date, trastuzumab may have a role in the treatment of primary breast cancer. However, the Committee considered that, with the data provided, they were unable to determine the optimum schedule and duration of trastuzumab treatment, the magnitude of treatment benefit on Overall Survival and, therefore, the cost-effectiveness of trastuzumab.

11.21. Given the high cost of trastuzumab, the early nature of the clinical data, and the significant impact on other services and investments in healthcare, which may offer better health outcomes for the money invested, the Committee did not consider it appropriate to make a recommendation for funding this product at this time. It noted that although there was insufficient evidence to make a positive recommendation at this time, it was likely that further data would enable the Committee to address it's questions regarding the long-term health benefits, optimal scheduling and cost-effectiveness of trastuzumab.

11.22. The Committee noted that it would welcome any substantial body of evidence from the supplier for consideration at subsequent meetings.