

**Appendix Five. PTAC minutes relating to trastuzumab for early breast cancer at its February, May, August and November 2006 and February 2007 meetings.**

**PTAC Meeting – 15 & 16 February 2006**

*(paragraph 20.19 as amended by PTAC in May 2006)*

**Trastuzumab (Herceptin)**

The Committee considered an application from Roche relating to the use of trastuzumab (Herceptin) for early breast cancer. The Committee noted that trastuzumab has not been registered for use in early breast cancer, although Roche had submitted an application to Medsafe. Members further noted that trastuzumab had not yet been licensed for this indication in any other country. The Committee noted that it was unusual for PTAC to consider applications for unregistered medicines or for unregistered indications of registered medicines. However, PTAC noted the high level of public concern and considered that they could give a preliminary view.

The Committee noted that the application was for adjunctive treatment of HER2-positive early breast cancer for patients who have previously undergone surgery and a course of chemotherapy. Members noted that trastuzumab is currently registered and funded for the treatment of metastatic disease.

The Committee noted that patients with HER2-positive breast cancer (around 20%) have a poorer prognosis than for patients with other breast cancers, with an average survival of approximately 50% after ten years.

The Committee noted that the submission focused primarily on two studies published recently in the New England Journal of Medicine, the first by Piccart-Gebhart et al – reporting interim results of the HERA trial, and the second by Romond et al – reporting a pooled analysis of data from study B-31 and partial results of study N9831. The Committee noted that all studies were open label.

**Piccart-Gebhart et al (HERA trial)**

Members considered the paper by Piccart-Gebhart et al (N Engl J Med. 2005 Oct 20; 353(16): 1659-72.), an interim analysis after 1 year of a planned 2-year study. Members noted that this was an unblinded study.

The Committee noted that the HERA trial was divided into three treatment arms:

- Arm 1: trastuzumab for one year (1694 patients)
- Arm 2: trastuzumab for two years (1694 patients)
- Arm 3: observation (1693 patients)

Members noted that the HERA trial results were analysed early, and that the paper reported only the results from arm 1 and arm 3. The Committee considered that the interim results from the second arm should also have been available to the authors, but noted that they were not included in the analysis.

The Committee noted that the primary measure in the HERA trial was disease-free survival; secondary measures included cardiac safety, overall survival, site of first disease-free survival event and time to distant recurrence.

The Committee noted that for patients followed up to two years (16% of enrolled patients) there was an 8.4% absolute increase in disease-free survival in the trastuzumab arm although there was, as expected, no significant increase in overall survival. Members further noted that 98% of patients enrolled in the study were alive at two years.

Members noted that there were fewer distant metastases in patients treated with trastuzumab, although there appeared to be an increased incidence of central nervous system metastases in patients treated with trastuzumab. Approximately one quarter of women in the trastuzumab arm who developed distant disease had central nervous system metastases.

The Committee noted that there was an increase in heart failure with trastuzumab and that at two years, 0.5% of patients in the treatment arm had developed moderate to severe (NYHA grade III or IV) heart failure

(0% in placebo group). 7.1% experienced a decrease in left ventricular ejection fraction (LVEF) compared with 2.2% in the observation arm. Members noted that, in addition, 143 patients (8.5%) withdrew from the trastuzumab arm, most withdrawals appeared to follow adverse events. Members considered that it was not clear from the report whether these patients were included in the reported heart failure events.

The Committee noted that in the study, patients had their cardiac function assessed immediately following chemotherapy, and patients were excluded from commencing therapy with trastuzumab if their LVEF was less than 55%. Members noted that in New Zealand, patients could typically wait up to six months for an echocardiogram. This could mean that, if patients were to begin treatment with trastuzumab immediately following chemotherapy, they could possibly be doing so without having their cardiac function assessed. Members considered that this was an issue that would need to be addressed, should DHBs decide to fund trastuzumab for early breast cancer.

Members noted that they would like to review the 1-year data from the 2-year trastuzumab arm, and the longer-term data of the other arms when available.

### **Romond et al**

Members considered the paper by Romond et al (N Engl J Med. 2005 Oct 20; 353(16): 1673-84.), pooled results of study B-31 and some of the results of N9831. Members noted that these studies were divided into the following treatment arms:

#### B-31

Arm 1: 12 weeks of paclitaxel

Arm 2: 12 weeks of paclitaxel plus trastuzumab for one year (started at same time)

#### N9831

Group A: 12 weeks of paclitaxel

Group B: 12 weeks of paclitaxel then trastuzumab for one year

Group C: 12 weeks of paclitaxel plus trastuzumab for one year (started at the same time)

The Committee noted that the results of each trial had not been published separately, and considered that, rather than a pooled analysis being published, each trial should have been published individually, with a subsequent meta-analysis (not a pooled analysis). Members noted that there were some significant differences between the papers that make comparison difficult, such as the timing of paclitaxel and the use of hormonal and radiation therapies. Members also noted that both trials were unblinded.

The Committee noted that the results of Group B of study N9831 were not included in the report, and that this was the only arm in the two studies that was of direct relevance to the application. Members considered that the efficacy results of this paper are of limited value.

The Committee noted that at median follow-up (2 years) there was a 9.6% absolute increase in disease-free survival in the trastuzumab arm, an 11.7% increase by three years, and by 4 years of follow-up an 18.2% increase. Members noted, however, that the 4-year follow-up data were based on relatively few patients; 165 patients (5% of the 3351 enrolled in the studies) had data out to 4 years, with 133 alive at that time.

The Committee considered that while it was possible that disease-free survival could translate into overall survival in the long-term, there was insufficient evidence upon which to extrapolate this benefit reliably. However, the Committee noted that there were 62 deaths in the trastuzumab arm and 92 in the control arm of the report, with an overall survival increase of 2.5% at three years, and 4.8% at four years.

The Committee noted that adverse cardiac events for each trial were reported separately. In trial B-31 there was an increased rate of severe (NYHA III or IV) heart failure or death at 3 years, of 4.1% in the trastuzumab arm versus 0.8% in the observation arm. In trial N9831, the rate of severe (NYHA III or IV) heart failure or death was 2.9% in the trastuzumab arm versus 0% in the observational arm. The Committee noted further that the pooled rate of discontinuation in this paper was even higher than in the HERA trial, with 364 (31.4%) patients having discontinued treatment with trastuzumab in the first year, 164 (14.2%) due to asymptomatic decreases in LVEF and 54 (4.7%) due to symptoms of cardiac failure or other adverse cardiac effect). Members also noted that patients taking trastuzumab appeared to have an increase in adverse respiratory side-effects, with four patients in trial B-31 developing interstitial pneumonitis, one of whom died.

## **General**

The Committee considered that the long-term cardiac safety of trastuzumab is unclear, and that there is insufficient evidence to indicate whether the risks are dose-related, or if they are reversible upon cessation of treatment.

The Committee considered that both the benefit and safety data for trastuzumab in early breast cancer were premature at present.

The Committee noted that the increased risk of heart failure would also be present when used in metastatic disease, but that in this situation the risk/benefit ratio is considered to be acceptable. Members noted that with early disease around 50% of patients are still alive after 10 years, whereas with metastatic disease none would be alive at this time – therefore consideration of the long-term risk of severe heart failure is more important when treating early disease than in metastatic disease. The Committee considered that in the case of early disease, the addition of trastuzumab could put at risk patients who would otherwise have survived.

The Committee considered that if trastuzumab was to be used for early breast cancer, then that patient's cardiac status would need to be monitored throughout treatment, and that there would be resultant increases in non-pharmaceutical expenditure.

The Committee noted that discontinuation rates for those undergoing trastuzumab in the trials were reasonably high, and that this was despite strict exclusion criteria and high levels of monitoring.

The Committee noted that the projected \$30 million cost per year was based on one year of treatment per patient, but noted that the trial data for two years would be available soon, and might indicate that there was a significant benefit in longer treatment. If this was the case the cost would be in the nature of \$60 million per year.

One member noted that there may be other priorities for breast cancer control that may confer greater population health gains than by funding trastuzumab to the above extent. These might include improved access to services and earlier presentation, diagnosis and follow up in order to reduce the numbers of patients presenting with more advanced breast disease.

The Committee considered that it could not recommend listing at this time. Members considered that before making a recommendation, the Committee should wait until trastuzumab received approval from Medsafe for use in early disease.

The Committee **recommended** that in the meantime, to maintain progress with the application for funding, PHARMAC staff should request that Roche supply the individual results of the trials B-31 and N9831, a meta-analysis (not pooled) of those two trials, and details of complete follow-up of all patients in all three studies considered to date, including all-cause mortality.

The Committee **recommended** referring the application to CaTSoP once these have occurred. The CaTSoP recommendation will then be taken to PTAC for a final listing recommendation.

## **PTAC Meeting – 25 May 2006**

### **Trastuzumab (Herceptin) – additional information requested**

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.

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**

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**

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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**

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.

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.

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.

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**

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**

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.

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 its questions regarding the long-term health benefits, optimal scheduling and cost-effectiveness of trastuzumab.

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

## PTAC Meeting – 17 August 2006

### Herceptin new data

PTAC has twice considered trastuzumab for the treatment of early HER-2 positive breast cancer at its meetings of February and May 2006. These minutes should be read in conjunction with the February and May 2006 minutes found at <http://www.pharmac.govt.nz/pdf/ptacmins.pdf>

The Committee reviewed further information in support of a submission from Roche Pharmaceuticals for the listing of trastuzumab (Herceptin) on the Pharmaceutical Schedule for the treatment of early HER-2 positive breast cancer.

The Committee reviewed the following material:

- Roche Pharmaceuticals' response to previous PTAC and CaTSOP minutes regarding trastuzumab;
- A technology appraisal from the University of Sheffield School of Health and Related Research (SchHARR) commissioned by the National Institute of Clinical Excellence (NICE);
- Two year median follow-up of the one year treatment arm of the HERA trial in the format of a PowerPoint slide presentation from the American Society of Clinical Oncology (ASCO) 2006 conference;
- "Adjuvant Docetaxel or Vinorelbine with or without trastuzumab for Breast Cancer", *Heikki Joensuu et al.* (N Engl J Med 354;8, February 23 2006), the "FinHer study".

### Correspondence from Roche Pharmaceuticals

The Committee noted Roche New Zealand's willingness to assist PHARMAC in the provision of evidence to support the use of trastuzumab.

The Committee expressed disappointment that additional trial data is unlikely to be available in a peer reviewed, published format in the near future.

### SchHARR report

The Committee noted that the SchHARR report was very comprehensive and raised similar concerns regarding the costs and benefits of trastuzumab that had been highlighted in PHARMAC's own cost utility analysis and previous PTAC minutes.

Members noted that the final recommendation of the SchHARR report did not appear to correlate to specific findings of the report.

### ASCO 2006 slide presentation for the HERA study

The Committee noted the limitations of clinical data presented as a PowerPoint slide presentation, which have not been subjected to external peer review for a reputable scientific journal. The Committee reiterated its view that it does not consider slide presentations alone to be adequate for the purpose of making important clinical recommendations.

The Committee noted that after a median follow-up of one year, as presented in Piccart-Gebhart et al (N Engl J Med. 2005 Oct 20; 353(16): 1659-72.), there was a reported absolute increase in two-year disease-free survival of 8.4% in the trastuzumab arm compared with control. The Committee noted that the slides indicated that after a median follow-up of two years the absolute increase in disease-free survival at three years in the trastuzumab arm compared with control had been reduced to 6.3%.

The Committee noted that the slides indicated that after two years follow-up the absolute overall survival difference at three years from randomisation, as displayed, was 2.7% in the trastuzumab arm against control, and appeared to be statistically significant. Members noted that this translated into a number needed to treat (NNT) of 37 patients.

The Committee considered that in an adjuvant setting an ongoing treatment effect would be expected with efficacy differences becoming greater over time. The Committee considered, however, that the difference in

the HERA treatment groups would have been anticipated to continue to diverge, rather than converge, which appears to be the case from the slide data presented. The Committee noted that 861 patients in the non-trastuzumab arm switched to trastuzumab after 12 months. Members noted that some of the convergence seen may have been due to the loss of patients from the observation arm, although there was insufficient data presented in the slides to clarify this.

Members noted that switching of patients from the observation arm to trastuzumab treatment meant that the validity of the long-term efficacy and safety profile of trastuzumab from the HERA trial may be significantly compromised. Members noted that although half of the patients in the observation arm who had not switched over by two years would be able to be measured in subsequent years, they would no longer necessarily be representative of all patients randomised to the observation arm. Members noted that this inconsistency would only be rectified by maintaining intention-to-treat analysis of the efficacy of trastuzumab beyond the one year.

The Committee noted that in data presented as 'censored', (data that excluded patients who had switched from control to trastuzumab), the denominators were not small enough to account for removal of all switched patients. The Committee concluded that this apparent inconsistency would likely be addressed in a formal peer-reviewed publication of this data and highlighted the difficulties of evaluating clinical data from a slide presentation.

### **The FinHer study**

The Committee considered that the FinHer study cast doubt over the optimal duration and timing of trastuzumab treatment. The Committee noted that the cost utility of trastuzumab use as per the FinHer protocol (9 weeks treatment) was likely to be appreciably better than 12 months treatment.

The Committee considered that the number of patients treated in the FinHer study (232) was substantial compared to many other cancer treatment trials.

The Committee noted that although HERA was a far larger trial, the number of patients treated in FinHer was not insignificant, and therefore the data from FinHer was valuable.

The Committee considered that the trastuzumab regimen used in the FinHer study resulted in comparable health gains to the regimen used in the HERA trial (11.7% absolute reduction in disease recurrence at three years against no trastuzumab), but produced less cardiotoxicity and other side effects, and was associated with a significantly reduced pharmaceutical and service cost.

The Committee considered that funding of trastuzumab as per the FinHer protocol (9 weeks treatment) could be considered.

### **Recommendations**

The Committee **recommended** that the application for the funding of trastuzumab as per the HERA protocol (12 months treatment) be declined due to the uncertainty surrounding long term clinical benefits and risks; the uncertainty over optimal duration of treatment; and the high budgetary impact associated with treatment.

The decision criteria relevant to PTAC's recommendation were: (i) The clinical benefits and risks of pharmaceuticals; (v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget).

The Committee **recommended** that the application be referred back to the Cancer Treatment Subcommittee of PTAC to consider the clinical appropriateness of any funding regimen consistent with the FinHer protocol (9 weeks treatment).

## PTAC Meeting – 15 & 16 November 2006

### Review of Sub-committee Records - Cancer Treatments Subcommittee (CaTSoP) – 26 / 27 October 2006

PTAC noted and accepted the minutes of the Cancer Treatments Sub-Committee of PTAC (CaTSoP) meeting held on 26 / 27 October 2006, with the following comments:

PTAC was cognisant of the promising preliminary data for trastuzumab and the need for more effective treatment options in this patient population.

However, PTAC reiterated that there was still uncertainty about the best way of administering trastuzumab in terms of optimal treatment duration, dose and schedule (sequential to, or concurrent with, chemotherapy), minimising cardiovascular toxicity and long-term clinical outcomes.

PTAC noted CaTSoP's discussion and recommendations regarding trastuzumab. The Committee noted that PHARMAC's amended base-case cost-utility analysis resulted in an indicative cost/QALY of \$12,300-\$29,200 for 9 weeks trastuzumab treatment as equivalent to the FinHer trial regimen; however, the Committee noted that this did not include the additional cost of docetaxel that was used in FinHer. PTAC noted that the absolute disease-free survival for trastuzumab-treated patients in the FinHer trial was 89% at three years, whereas the published absolute disease free survival in the HERA trial was 86% (95% confidence interval 83%-89%) at a median duration of one year.

The Committee considered that more clinical research was needed and that a study comparing 12 months trastuzumab with 9 weeks trastuzumab should be performed.

The Committee noted CaTSoP's view that, in the absence of availability of funding for 12 months trastuzumab treatment, 9 weeks treatment would be reasonable. PTAC **recommended** that, subject to an acceptable cost/QALY, including the cost of docetaxel, 9 weeks treatment with trastuzumab should be funded and gave this recommendation a high priority.

The Committee considered that the relevant decision criteria in favour of this recommendation were *(i) the health needs of all eligible people within New Zealand, (ii) The particular health needs of Maori and Pacific peoples (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things, (iv) The clinical benefits and risks of pharmaceuticals, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule and (viii) the Government's priorities for health funding.*

## PTAC Meeting – 21 & 22 February 2007

### Trastuzumab (Herceptin) for HER2 positive early breast cancer

The Committee considered further information in relation to the application from Roche for the use of trastuzumab in HER2 positive early breast cancer. The Committee noted that this had been considered previously by PTAC at its February, May, August and November 2006 meetings. These minutes should be read in conjunction with the previous minutes found at <http://www.pharmac.govt.nz/pdf/ptacmins.pdf>.

The Committee reviewed the following material:

- 6 January 2007 Lancet publication of the two-year median follow-up of the one-year treatment arm of the HERA trial (Smith et al) and the accompanying editorial (Hind et al);
- Power point presentation 'Phase III Trial Comparing AC-T with AC-TH and with TCH in the Adjuvant Treatment of HER2 positive Early Breast Cancer Patients: Second Interim Efficacy Analysis' BCIRG006 Trial; Slamon et al, presented at the San Antonio Breast Cancer Symposium (SABCS) 14-17 December 2006;
- Poster presentation 'Adjuvant Trastuzumab: Long-Term Results of E2198' Sledge et al, SABCS December 2006;
- 'Trastuzumab in Early Stage Breast Cancer' Huybrechts M, Hulstaert F, Neyt M, Vrijens F, Ramaekers D. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2006. KCE reports 34C (D/2006/10.273/25)
- New Zealand, Australian and USA trastuzumab Datasheets

The Committee noted that at its November 2006 meeting it considered that more clinical research was needed and that a study comparing 12 months trastuzumab with 9 weeks trastuzumab should be performed. The Committee further noted it **recommended** that, subject to an acceptable cost/QALY, including the cost of docetaxel, 9 weeks treatment with trastuzumab should be funded and gave this recommendation a high priority.

#### The Lancet article and editorial – 2-year median follow-up HERA data

The Committee noted that the two-year median follow-up data published in the Lancet in January 2007 confirmed the results presented at the American Society of Clinical Oncology (ASCO) 2006 conference that were considered by the Committee at its August 2006 meeting.

The Committee noted that data for patients treated with two years trastuzumab in the HERA trial is still to be reported.

The Committee noted that the hazard ratio (HR) for the two-year median follow-up was 0.64 (95% confidence interval 0.54-0.76), compared with the one-year median follow-up HR of 0.54 that had been considered by the Committee and used in PHARMAC's cost-utility analysis of trastuzumab. The Committee considered that these two-year follow-up data indicated a possible waning of treatment effect compared with the previous one-year follow-up data, and noted that the graphs in the Lancet paper indicated a possible convergence in disease-free survival between the sequential trastuzumab and standard treatment arms after the first six months' follow-up.

The Committee noted that 55 patients would need to be treated to prevent one death after two years' median follow-up ('number needed to treat' (NNT)), and that one of every 51 patients would suffer an adverse cardiac event over the same time period ('number needed to harm' (NNH)). The Committee noted that this NNH would reduce to one in 20 patients having any form of cardiac toxicity including non-symptomatic reductions in left ventricular ejection fractions (LVEF).

The Committee noted that the study design of HERA allowed switching of patients from the observation arm to trastuzumab treatment after publication of the one-year follow-up data. It was noted that 861 out of 1698 patients in the original observation treatment group had switched to trastuzumab. The Committee reiterated

that due to this non-randomised switching the control group had been 'lost'; therefore, interpretation of future long-term efficacy and safety data for trastuzumab in this study would be significantly compromised.

#### **BCIRG006 trial results**

The committee reviewed 36-month median follow-up data from the Breast Cancer International Research Group (BCIRG) 006 study (as yet unpublished) as an interim analysis supplied in the form of MS PowerPoint slides of a presentation at SABCS in December 2006. The Committee noted that it had reviewed an interim analysis of 23-months median follow-up data during its May 2006 Meeting. The Committee 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 (AC-T); the second containing the same chemotherapy regimen plus one year of trastuzumab commenced concurrently with docetaxel (AC-TH); and the third comprising six cycles of docetaxel and carboplatin with one year of trastuzumab commenced concurrently with the chemotherapy (TCH).

The Committee noted that there was a significant improvement in both disease-free and overall survival in the trastuzumab treated patients in this study. The Committee considered that there appeared to be no clinical difference between the AC-TH (containing the anthracycline doxorubicin) treated patients compared with TCH (containing no anthracycline) treated patients, although the slide presentation did not present the results of a formal statistical comparison between the two arms. Members noted, however, that cardiac toxicity was lower in the TCH treatment group; therefore, it questioned the clinical benefit of anthracycline use in this study.

#### **E2198 trial results**

The Committee reviewed the 5-year follow-up results of study E2198 presented as a poster at SABCS in December 2006. This study compared short-duration trastuzumab (10 weeks) given concurrently with paclitaxel prior to anthracycline treatment, with the same treatment plus an additional 52 weeks trastuzumab after completion of anthracycline treatment.

The Committee noted similar clinical outcomes in the short-duration concurrent regimen compared with the extended (52 weeks) trastuzumab treatment. The Committee considered that although the study was not designed to test efficacy, and was not powered to determine equivalence, the results supported the efficacy of short-duration concurrent trastuzumab therapy when administered before anthracycline containing chemotherapy, as demonstrated in the FinHer study, and supported the rationale for the SOLD study which would compare long versus short durations of concurrent trastuzumab regimen.

#### **New Zealand Datasheet, Australian Product Information and USA Prescribing Information**

The Committee noted that a key issue around its recommendation for funding 9 weeks treatment with trastuzumab (concurrent with chemotherapy) is that this treatment regimen is not currently covered by the Medsafe-approved Datasheet in New Zealand which specifies that trastuzumab is to be administered following completion of adjuvant chemotherapy (i.e. sequential treatment).

The Committee noted that the USA Prescribing Information recommends that trastuzumab is administered for 12 months starting concurrently with paclitaxel and that the Australian Product Information allows for 12 months sequential, 12 months concurrent or 9 weeks concurrent treatment regimens to be used.

The Committee specifically noted that the Australian Product Information states that 'The optimal dosage regimen and treatment duration have not been defined. A favourable risk/benefit ratio has been demonstrated with the following regimens:

- Three weekly regimen (HERA trial): Treatment with HERCEPTIN was commenced following surgery and completion of neoadjuvant or at least 4 cycles of adjuvant chemotherapy.
- Weekly regimen (B31/N9831 trials): Treatment with HERCEPTIN was commenced following surgery and completion of 4 cycles (12 weeks) of doxorubicin and cyclophosphamide (AC) chemotherapy, then together with paclitaxel for 12 weeks, then as a single agent for a further 40 weeks.
- Weekly regimen (FinHer trial): Treatment with HERCEPTIN was commenced following surgery and was given concurrently with docetaxel or vinorelbine for a total of 9 weeks.'

The Committee considered that the Australian Product Information was consistent with its view that there was still uncertainty about the best way of administering trastuzumab.

The Committee noted that trastuzumab currently has provisional consent in New Zealand and, therefore, there may be an opportunity for Medsafe to align the New Zealand datasheet with that in Australia. The Committee resolved to write to Medsafe to request that it initiate a review of the datasheet, given the Committee's concerns that the datasheet specified sequential 12 months trastuzumab treatment, which the Committee considered may be inappropriate (given that the two-year median follow-up data from HERA, alongside the results of Arm B of study N9831, raised significant doubts about the magnitude of efficacy of sequential 12 months trastuzumab, and that concurrent regimens may be, at least as, if not more efficacious than sequential).

### **Cost-Utility Analysis**

The Committee received a verbal update from PHARMAC staff regarding the trastuzumab cost-utility analysis (CUA), which had been updated to indicate the cost-effectiveness of the nine-week concurrent treatment regimen (as per FinHer). The Committee noted that the updated analysis included the cost of docetaxel (Taxotere), and made the conservative assumption that the cardiotoxicity risks and costs would be the same as seen in the HERA trial (because FinHer may have been underpowered to detect these risks).

The Committee noted that the base-case results of the revised CUA were less than \$20,000/QALY under conservative scenarios for effectiveness. The Committee considered that the inputs for the revised CUA were sound and noted that the cost-effectiveness of nine-week concurrent treatment with trastuzumab was comparable to other pharmaceuticals funded by PHARMAC.

The Committee noted the Belgian Health Technology Assessment report and considered that the conclusions outlined in the report were reasonable and consistent with the Committee's views.

### **General Discussion**

The Committee reiterated its view that there was still uncertainty about the best way of administering trastuzumab in terms of optimal treatment duration, dose and schedule (sequential to, or concurrent with, chemotherapy), minimising cardiovascular toxicity, and long-term clinical outcomes.

Specifically, the Committee considered that data from Arm B of study N9831 raised significant doubts about the efficacy of sequential 12 months trastuzumab. The Committee noted that it had requested in May 2006 that full data from the N9831 trial be provided by the supplier, but thus far this had not been provided. The Committee considered that there was now likely to be longer-term follow-up of outcomes (disease free survival and mortality) in this study, and that all the updated data from all three arms of the trial should be made available to the Committee.

The Committee reiterated its **recommendation** from its November 2006 meeting that 9 weeks treatment with trastuzumab (concurrent with chemotherapy and before anthracycline) should be funded and gave this recommendation a high priority.

The Committee considered that more clinical research was needed to determine if long duration concurrent treatment (52 weeks) is any better than short duration concurrent treatment (9 weeks) and reiterated that a comparative study should be performed. The Committee noted CaTSoP's advice from its October 2006 meeting that the proposed SOLD study was well designed and would answer some of the questions relating to the optimal dose, duration and scheduling of trastuzumab in early HER2 positive breast cancer.