Timeline of PHARMAC’s Work on Herceptin

The following summary outlines PHARMAC’s work to date:

- **July 2008**: PHARMAC Board declines funding for 12 months Herceptin for HER 2 positive early breast cancer. Concurrent 9 week Herceptin treatment is a full treatment course and remains fully funded.
- **4 July 2008**: PTAC considers new information on Herceptin. PTAC reconfirms its earlier recommendation that funding for 12 months treatment be declined.
- **13 June 2008**: CaTSoP considers new information on Herceptin.
- **10 June 2008**: Consultation ends. More than 300 submissions are received. Media Release - Herceptin consultation ends (3 pages, 121 KB)
- **17 May 2008**: Leading international medical journal The Lancet publishes a commentary by NZ and international clinicians and researchers (including the PTAC Chair and PHARMAC staff) about publication bias with Herceptin for HER 2 positive early breast cancer. The article claims that Herceptin, as used throughout much of the world (12 months sequential treatment) is much less effective than thought because important clinical trial data from nearly 1000 women are in effect missing. The Lancet ‘Trastuzumab: possible publication bias’ (7 pages, 350 KB), with the & definitive version on the Lancet website
- **5 May 2008**: Q&A Herceptin Background (5 pages, 57 KB)
- **5 May 2008**: Media Release - Herceptin consultation underway (9 pages, 177 KB)
- **2 May 2008**: PHARMAC consults on proposal to decline 12 months’ Herceptin funding for HER 2 positive early breast cancer. Consultation on proposal regarding the funding of 12 months treatment with trastuzumab for HER 2 positive breast cancer (4 pages, 222 KB)
- **3 April 2008**: High Court issues ruling on judicial review application, and upholds one of the 28 grounds for judicial review. PHARMAC is directed to consult on its decision not to funding 12 months' Herceptin in July 2006. High Court judgement on judicial review of PHARMAC's Herceptin decisions (74 pages, 186 KB)
- **February 2008**: High Court hearing on judicial review application takes place over 6 days.
- **24 August 2007**: The NZ Medical Journal publishes further material by PHARMAC staff responding about the basis for and evidence supporting the nine week concurrent Herceptin funding decision. PHARMAC responds to Isaacs et al in NZ Medical Journal. (7 pages, 103 KB)
- **August 2007**: High Court hears application for interim orders on these proceedings. Finds in favour of PHARMAC.
- **1 July 2007**: Herceptin funded for women with HER 2 positive early breast cancer.
- **29 June 2007**: Eight women file proceedings in the High Court seeking judicial review of PHARMAC'S Herceptin decisions.
- **15 June 2007**: The NZ Medical Journal publishes a Special Series article by PHARMAC staff about the funding of nine week concurrent Herceptin. New Zealand Medical Journal article (20 pages, 263 KB) (published 15 June 2007;120(1256), provided here with the Journal's permission). The appendices to the NZMJ article also give more information on HER2-positive early breast cancer and survival (Appendix 1 (6 pages, 67 KB)), epidemiology and ethnic disparities (Appendix 2 (6 pages, 61 KB)), clinical trials (Appendix 3 (1 page, 26 KB)), clinical effectiveness (Appendix 4 (41 pages, 1015 KB)), PTAC minutes (Appendix 5 (12 pages, 106 KB)), and compare the 12 month and 9 week regimens (Appendix 6 (3 pages, 28 KB)).
- **3 May 2007**: Cost utility analysis released under the Official Information Act: TAR 75 Trastuzumab (Herceptin) in HER-2 positive early breast cancer with 9 week regimen CUA (66 pages, 566 KB), Appendix 1 (8 pages, 164 KB), Appendix 2 (2 pages, 124 KB), Appendix 3 (1 page, 61 KB), Appendix 4 (3 pages, 63 KB), Appendix 5 (8 pages, 177 KB), Appendix 6 (14 pages, 511 KB).
3 May 2007: Notification of widened access to trastuzumab (Herceptin) and docetaxel (Taxotere) on the Pharmaceutical Schedule for adjuvant treatment of HER2 positive early breast cancer (3 pages, 149 KB)

3 May 2007: Herceptin Questions and answers May 2007 (3 pages, 133 KB)

3 May 2007: media release: 350 women each year to benefit from Herceptin funding decision (2 pages, 73 KB)

April 2007: PHARMAC Board approves funding for concurrent 9 weeks' treatment with Herceptin for HER2 positive early breast cancer from 1 July 2007.

Early March 2007: Following consultation with DHBs, public consultation occurs on a draft proposal (see consult letter (3 pages, 101 KB) and media release (3 pages, 114 KB)) to fund Herceptin (concurrent nine weeks). The Consumer Advisory Committee recommends the development of a patient resource relating to any funding decision.

22 February 2007 (22 pages, 186 KB): PTAC examines further information from Roche on Herceptin. Reiterates recommendation that concurrent nine weeks' treatment be funded.

16 February 2007: PHARMAC commits to supporting the SOLD clinical trial.

In early 2007: PHARMAC re-examined all the available evidence on Herceptin. This assessment is summarised in this PHARMAC presentation. Background information and answers to questions are available here (3 pages, 133 KB).

December-February 2006-07 (3 pages, 30 KB): Cost utility analysis of nine week treatment undertaken by PHARMAC; investigation of NZ participation in international clinical trial.

November 2006 (18 pages, 150 KB): PTAC receives CaTSOP minute. PTAC recommends concurrent nine week treatment be funded (high priority). PTAC also notes more clinical research is needed (specifically a study comparing concurrent 12 months' treatment with 9 weeks').

October 2006: CaTSOP meets. Recommends that in the absence of funding for 12 months, 9 weeks' Herceptin treatment would be reasonable.

August 2006 (16 pages, 198 KB): Further data on Herceptin considered by PTAC. PTAC asks CaTSOP to consider clinical appropriateness of any funding regimen consistent with a nine-week treatment of Herceptin.

June/July 2006 (5 pages, 46 KB): DHBs and PHARMAC decide not to fund Herceptin at that time, and commit to an ongoing review of Herceptin.

25 May 2006 (18 pages, 164 KB): CaTSOP recommendation provided to PTAC. PTAC considered there was insufficient evidence to justify a funding recommendation for 12 months treatment, and sought further information.

April-June 2006: Negotiations occur with Roche regarding supply terms and pricing.

April 2006: Cancer Treatments Sub-Committee (CaTSOP) reviews Roche's Herceptin application.

March-May 2006: Cost-utility analysis of 12 months' treatment with Herceptin for HER2 positive early breast cancer prepared by PHARMAC.

23 March 2006: @Medsafe grants provisional consent to Herceptin for treatment for HER2 positive early breast cancer.

18 February 2006 (2 pages, 444 KB): The Pharmacology and Therapeutics Advisory Committee (PTAC) considers application from Roche. PTAC recommends further information be sought from Roche and for Herceptin to be considered by the cancer treatments sub-committee, should Herceptin be approved by Medsafe.

December 2005: PHARMAC receives application from Roche to fund Herceptin for 12 months' sequential treatment for HER2 positive early breast cancer (an indication not then approved by @Medsafe).
### Appendix Nine: Updated trastuzumab (Herceptin) clinical trial summaries

#### Sequential treatment trials, long duration (12 month)² regimens

<table>
<thead>
<tr>
<th>Patient Numbers</th>
<th>HERA</th>
<th>N9831 Arm B</th>
<th>PACS04*</th>
<th>B31*</th>
<th>N9831 Arm C*</th>
<th>BCIRG006*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observation:</strong></td>
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<tr>
<td>1,693</td>
<td></td>
<td>1,693</td>
<td>985</td>
<td>1,019</td>
<td>1,694</td>
<td></td>
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<tr>
<td><strong>Trastuzumab (1 yr):</strong></td>
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<tr>
<td>1,694</td>
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<td>979</td>
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<tr>
<td><strong>Trastuzumab (2 yr):</strong></td>
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<tr>
<td>1,694</td>
<td>985</td>
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</table>

#### Intervention

<table>
<thead>
<tr>
<th>1 loading dose (8mg/kg) trastuzumab, then 6mg/kg every 3 weeks for one year or two years</th>
<th>1 loading dose (4mg/kg) trastuzumab, then 2mg/kg every week for 52 weeks²</th>
<th>1 loading dose (4mg/kg) trastuzumab, then 2mg/kg every week for 52 weeks²</th>
<th>1 loading dose (4mg/kg) trastuzumab, then 2mg/kg every week for 52 weeks²</th>
<th>9 trastuzumab infusions at 1 week intervals. First dose 4mg/kg, remaining doses 2mg/kg</th>
</tr>
</thead>
</table>

#### Timing of treatment

<table>
<thead>
<tr>
<th>Sequential (after completion of all chemotherapy – anthracycline chemotherapy² and taxane treatment)³</th>
<th>Concurrent with taxane (paclitaxel), after completion of anthracycline chemotherapy</th>
<th>Concurrent with taxane (docetaxel) treatment, before anthracycline chemotherapy⁴</th>
</tr>
</thead>
</table>

#### Disease free survival (DFS) hazard ratio (HR) (95% confidence interval)

<table>
<thead>
<tr>
<th>12-mth median follow-up (mfu):</th>
<th>1.5-yr mfu:</th>
<th>4-yr mfu:</th>
<th>2.4-yr mfu:</th>
<th>1.5-yr mfu:</th>
<th>22-mth mfu:</th>
<th>36-mth mfu:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.54 (0.43-0.67)</td>
<td>0.67 (0.67-1.13)</td>
<td>0.66 (0.61-1.22)</td>
<td>0.45 (0.35-0.58)</td>
<td>0.55 (0.36-0.76)</td>
<td>0.49 (0.37-0.79)</td>
<td>0.42 (0.21-0.83)</td>
</tr>
<tr>
<td>0.64 (0.54-0.76)</td>
<td>0.67 (0.67-1.13)</td>
<td>0.66 (0.61-1.22)</td>
<td>0.45 (0.35-0.58)</td>
<td>0.55 (0.36-0.76)</td>
<td>0.49 (0.37-0.79)</td>
<td>0.42 (0.21-0.83)</td>
</tr>
</tbody>
</table>

#### Overall DFS HR (95% CI)

<table>
<thead>
<tr>
<th>12-mth mfu:</th>
<th>1.5-yr mfu:</th>
<th>4-yr mfu:</th>
<th>Not reported</th>
<th>36-mth mfu:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72 (0.67-0.78)</td>
<td>0.67 (0.67-1.13)</td>
<td>0.66 (0.61-1.22)</td>
<td>0.45 (0.35-0.58)</td>
<td>0.42 (0.21-0.83)</td>
</tr>
</tbody>
</table>

#### Overall survival (OS) HR (95% CI)

<table>
<thead>
<tr>
<th>12-mth mfu:</th>
<th>1.5-yr mfu:</th>
<th>4-yr mfu:</th>
<th>Not reported</th>
<th>36-mth mfu:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.76 (0.47-1.23)</td>
<td>0.65 (0.55-1.33)</td>
<td>0.60 (0.61-0.99)</td>
<td>0.45 (0.35-0.58)</td>
<td>0.42 (0.21-0.83)</td>
</tr>
</tbody>
</table>

#### Overall OS HR (95% CI)

| 0.76 (0.65-0.88) | 0.63 (0.51-0.77) |

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¹ Updates to this table since TAR 75 (August 2006) and TAR 75b (April 2007) are indicated by red text.

**The six RCTs reporting disease outcomes for adjuvant trastuzumab compared with standard chemotherapy treatment alone in HER2-positive early breast cancer

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¹ No data have yet been reported for the outcomes of the 2 year trastuzumab treatment arm in the HERA trial.

² A seventh study, EC0X E2198, which compared 12 months with 10 weeks trastuzumab given concurrently with paclitaxel, was presented as a poster at the San Antonio Breast Cancer Symposium in 2006 (Sledge et al, http://www.abstractsandview.com/sabcs06/view.php?nu=SABCS06_LJ). However, this was a pilot study not designed to test efficacy nor powered to determine equivalence and has not reported outcomes against standard chemotherapy treatment.

³ The randomisation of patients to trastuzumab in PACS04 was a second randomisation applied specifically to the HER2 positive subpopulation (n=528 randomised). All patients in this trial (total n=3310) were initially randomised to receive either Arm A: 6 cycles of adjuvant 5-fluorouracil-epirubicin-cyclophosphamide (FEC100: F and C 500 mg/m², E 100 mg/m²), or Arm B: 6 cycles of concomitant ED (E and D 75 mg/m²) every 3 weeks. As soon as HER2 status was available, patients with HER2 positive tumours were randomised to Arm C: additional observation only, or Arm D: additional 1 year of trastuzumab (7) 8mg/kg loading dose, 6mg/kg qw4w. The primary endpoint was 3-year DFS for the C and D arms. The distribution of patients between the other chemotherapy treatments (FEC100, ED) in the HER2 positive subpopulation is not available.

⁴ Although reported jointly, the NSABP-B31 and NCCTG-N9831 trials of concurrent regimens differed in patient eligibility (high risk negative node status); methods of randomisation allocation; taxane regimens, anthracycline regimens, sequencing with radiotherapy, sequencing with hormonal therapy, aromatase inhibitor therapies, and when they started to be used in the trials; recommendations for post surgical radiotherapy; and primary endpoints (disease free survival for DFS for N9831, overall survival for B31). Note that there was also an arm to BCIRG006 (arm TCH) that consisted of 6 cycles of docetaxel and carboplatin with concurrent trastuzumab (i.e. no anthracycline chemotherapy). However, this regimen is not comparable to the other regimens, these results are not presented in this table. For further information regarding BCIRG006 see TAR 75 Appendix One: Minutes of the relevant clinical advisory committee meetings.

⁵ Anthracycline containing chemotherapy regimens (FEC or FAC).