PUBLIC SUMMARY DOCUMENT
Product: Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®.
Sponsor: Roche Products Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Item

The Department of Health and Ageing requested that the PBAC re-examine the clinical and cost-effectiveness evidence available for trastuzumab for metastatic breast cancer (MBC), including the current use in Australia, and provide advice to Government as to whether trastuzumab could be recommended for PBS listing for MBC.

2. Background

At the September 2000 PBAC meeting, the PBAC rejected a major submission to list trastuzumab for the treatment of patients with human epidermal growth factor receptor 2 (HER-2) positive metastatic breast cancer (a) in combination with taxanes for patients who have not received chemotherapy for metastatic disease; or (b) as monotherapy for patients who have received one or more chemotherapeutic regimens for their metastatic disease. The PBAC rejected the submission for combination therapy due to unacceptably high cost effectiveness due to the high cost of the drug. The submission for monotherapy was deferred to allow investigation of the cost effectiveness of the comparator drugs.

At the December 2000 meeting a minor re-submission, for both combination therapy and monotherapy was considered. The PBAC again deferred the submission in order to seek the sponsor's preparedness to offer a price reduction as the cost effectiveness ratios remained unacceptably high. A further re-submission was presented to the March 2001 PBAC meeting, however in the absence of an offer of a further price reduction as stipulated in the deferral of the application to the December 2000 meeting, the application was rejected.

At the September 2001 meeting the PBAC rejected an application for a Section 100 listing for the treatment of HER-2 positive patients with MBC, in combination with taxanes, for patients who have not received chemotherapy for their metastatic disease and as monotherapy for the treatment of those patients who have received one or more chemotherapy regimen(s) for their metastatic disease, because of unacceptable cost-effectiveness.

The Government established the Herceptin Program in December 2001. Funding for the Herceptin Program has been reviewed twice by Government since 2001 prior to this 2008 review request.

In 2004, the review recommended that the Program should continue but that steps should be taken to minimise wastage. The Department of Health and Ageing (the Department), following consultations with the Therapeutic Goods Administration (TGA) and oncologists, obtained authorisation in August 2005 to allow a three-weekly rather than weekly dosing regimen to improve convenience for patients and reduce drug wastage. In addition, Roche Products were requested to seek TGA registration of an additional vial size to reduce wastage. Registration has not proceeded to date.

In 2006, the review recommended that the program be funded for a further two years and that the Department evaluate the effectiveness and cost-effectiveness of trastuzumab for

metastatic breast cancer, and that the evaluation be considered by the PBAC and its recommendations made available to Government.

In the period from December 2001 to June 2008 total expenditure on the Herceptin Program was $212 million and 3193 women were treated.

Herceptin was listed for early stage breast cancer on the PBS from 1 October 2006. The total PBS expenditure to June 2008 was $100.7 million.

6. Comparator

The comparators were placebo or trastuzumab co-administered with the following regimens:

- taxanes (paclitaxel or docetaxel) ± other chemotherapy
- aromatase inhibitors
- vinorelbine

A clinical comparison of capecitabine with or without trastuzumab, and use of trastuzumab as monotherapy or beyond disease progression were presented, however these comparisons did not form the basis of the economic models.

It was noted that not all the trastuzumab combination therapies (e.g. combination with vinorelbine or capecitabine) have marketing approval by the TGA.

7. Clinical Trials

The key, randomised trials are summarised below.

Trastuzumab + taxane versus taxane alone: three randomised, open-label trials for first-line treatment of HER2 positive patients with advanced or metastatic breast cancer:

- Slamon 2001: trastuzumab + paclitaxel or paclitaxel only
- Marty 2005: trastuzumab + docetaxel or docetaxel only
- Gasparini 2006: trastuzumab + paclitaxel or paclitaxel only.

Trastuzumab + aromatase inhibitor versus aromatase inhibitor alone: one randomised, open-label trial for first and second-line treatment of post-menopausal women with HER2 positive, hormone receptor positive, MBC:

- TanDEM trial (B016216): trastuzumab + anastrozole vs anastrozole alone.

Trastuzumab + vinorelbine versus trastuzumab + taxanes: one randomised, open-label trial for first-line treatment of HER2 positive MBC:

- Burstein 2007: trastuzumab + vinorelbine vs trastuzumab + paclitaxel/docetaxel.

No head to heads trials of trastuzumab + vinorelbine versus vinorelbine alone were available in the first-line setting. A summary of non-randomised and single arm studies was presented as evidence for the trastuzumab monotherapy indication.

The studies published at the time of the review for the comparison of trastuzumab with a taxane versus taxane alone were:

Trial ID	Protocol/Publication Title	Publication citation

Direct randomised trials of trastuzumab+taxane versus taxane alone (first-line treatment)		
Trial H0648g	Use of chemotherapy plus a monoclonal antibody against HER 2 for metastatic breast cancer that over express HER2. Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: Effect of cardiac dysfunction on treatment outcomes in women receiving trastuzumab for HER2-overexpressing metastatic breast cancer.	Slamon D, Leyland-Jones B, et al. (2001). *The New England Journal of Medicine,* 344: 783-92. Eiermann W. (2001). Pivotal trial data. *Annals of Oncology*, 12 (Suppl 1): S57-S62. Tripathy D, Seidman A, et al. (2004). *Clinical Breast Cancer* 5 (4): 293-8.
Trial M77001	Randomized Phase II trial of the efficacy and safety of Trastuzumab combine with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first line treatment: Randomised phase II trial (M77001) of trastuzumab (Herceptin) plus docetaxel versus docetaxel alone, as first-line therapy in patients with HER2-positive metastatic breast cancer [abstract].	Marty M, Cognetti F, et al. (2001). The M77001 study group. *Journal of Clinical Oncology,* 23 (13): 4265-74. Extra JM, Cognetti F, et al. (2003). *European Journal of Cancer*, 1 (5): S202.
Trial report not available	Randomized Phase II trial of weekly paclitaxel alone versus trastuzumab plus weekly paclitaxel as first-line therapy of patients with HER2 positive advanced breast cancer.	Gasparini G, Gion M, et al. (2007). *Breast Cancer Res Treat*, 101: 355-65.
Comparative trial of trastuzumab+taxane versus chemotherapy alone (first-line treatment)		
Trial report not available	Use of the monoclonal antibody anti-HER2 trastuzumab in the treatment of metastatic breast cancer. A cost-effectiveness analysis.	Poncet B, Bachelot T, et al. (2008). *American Journal of Clinical Oncology*, 31: 363-8.
Trastuzumab + Taxane (second-line or subsequent treatment)		
Non comparative studies		
Trial report not available	Efficacy and safety of combined trastuzumab and paclitaxel therapy as a second-line treatment in women with metastatic breast cancer: a single institutional experience.	Furukawa K, Ito Y, et al. (2006). *Breast Cancer*, 13: 329-33.

The studies published at the time of the review for the comparison of trastuzumab + taxane + chemotherapy versus taxane + chemotherapy were:

Study	Protocol/Publication Title	Publication citation
Trastuzumab + taxane + chemotherapy studies		
Randomised trials		
Robert 2006, 2004, 2001	Randomized Phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER2-overexpressing metastatic breast cancer. Randomized phase III trial study of trastuzumab, paclitaxel, and carboplatin versus trastuzumab and paclitaxel in women with HER-2 overexpressing metastatic breast cancer: An	Robert N, Leyland-Jones B, et al. (2006). *Journal of Clinical Oncology*, Vol 24, No.18: 2786-92. Robert NJ, Leyland-Jones B, et al. (2004). *Annual Proceedings of the American Society of Clinical Oncology.*

	update including survival [abstract]. Toxicity profiles: a comparative study of Herceptin (trastuzumab) and Taxol (paclitaxel) versus Herceptin, Taxol, and carboplatin in HER-2 positive patients with advanced breast cancer.	Robert NJ, Slamon D, et al. (2001). *Breast Cancer Research and Treatment*, 69 (3): 304.
BCIRG 007	Randomised phase III trial of trastuzumab plus docetaxel plus docetaxel with or without carboplatin first line in HER2 positive metastatic breast cancer (MBC).	Forbes JF, Pienkowski T, et al. (2006). BCIRG 007: *Journal of Clinical Oncology*, ASCO Annual Meeting Proceedings (Post-Meeting Edition) 24 (18S) (June 20 Supplement) Pegram 2007. Slides that accompanied the abstract from ASCO 2007. BCIRG 007 study. First overall survival analysis of a multimeter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab s first line chemotherapy for patients with metastatic breast cancer containing the Her2/neu alteration.
Comparative study		
Tauer 2006	Randomized phase II trial of two different schedules of carboplatin (C) and paclitaxel (P) + trastuzumab (T) as first line treatment for metastatic breast cancer (MBC) [abstract].	Tauer K, Schwartzberg LS, et al. (2006). *Journal of Clinical Oncology*¸ ASCO Annual Meeting Proceedings (Post-Meeting Edition) 24 (18S) (June 20 Supplement).
Non comparative studies		
Pegram 2004	Results of two open-label, multicenter phase II studies of docetaxel, platinum salts and trastuzumab in HER2-positive advanced breast cancer	Pegram M, Pienkowski T, et al. (2004), *Journal of the National Cancer Institute,* 96 (10): 759-69.
Burris 2004	Phase II trial of trastuzumab followed by weekly paclitaxel/carboplatin as first-line treatment for patients with metastatic breast cancer.	Burris III H, Yardley D, et al. (2004). *Journal of Clinical Oncology*, 22 (9): 1621-9.
Perez 2005a	Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983552.	Perez E, Suman V. (2005). *Clinical Breast Cancer*, 6 (5): 425-32.
Taxane + carboplatin studies		
Single arm of randomised trials		
Fountzilas 2004	Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group.	Fountzilas G, Kalofonos H, et al. (2004), *Annals of Oncology* 15: 1517-26.
Non comparative studies		
Perez 2005b	A phase II trial of docetaxel and carboplatin as first-line chemotherapy for metastatic breast cancer: NCCTG study N9932.	Perez A, Suman V, et al. (2005)., *Oncology*, 69: 117-21.

Perez 2000	A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma.	Perez A, Hillman D, et al. (2000)., *Cancer*, 88: 124-31.
Ford 1997	A phase II study of repetitive cycles of dose-intense carboplatin plus paclitaxel chemotherapy and peripheral blood stem cells in metastatic breast cancer.	Ford C, Spitzer G, et al. (1997). *Seminars in Oncology*, 5 (Suppl 17): S-17-81-6.

Trast=trastuzumab, Pac=paclitaxel, TPC=trastuzumab + paclitaxel + carboplatin, TP=trastuzumab + paclitaxel, TDC=trastuzumab + docetaxel + carboplatin, TD=trastuzumab + paclitaxel, MBC=metastatic breast cancer, TTP=time to progression, OS=overall survival, +ve=positive

The studies published at the time of the review for the comparative effectiveness of trastuzumab + aromatase inhibitors and aromatase inhibitors alone were:

Trial ID	Protocol/ publication title	Publication citation
Non-comparative study		
Trastuzumab + letrozole		
Marcom 2007	The combination of letrozole and trastuzumab as first or second-line biological therapy produces durable responses in a subset of HER2 positive and ER positive advanced breast cancers.	Marcom P, Isaacs C, et al. (2007). *Breast Cancer Res Treat*, 102: 43-49.

ER=oestrogen receptor

The TaNDEM study was not published at the time of the review.

The studies published at the time of the review for trastuzumab + vinorelbine and vinorelbine alone in first-line treatment of metastatic breast cancer were:

Trial ID	Protocol/ publication title	Publication citation
Trastuzumab +Vinorelbine Studies		
Randomised trials		
Burstein 2007	Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexperessing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study.	Burstein H, Keshaviah A, et al. (2007). *Cancer*, 110(5): 965-72.
Non randomised studies		
Burstein 2003	Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: multicentre phase II trial with clinical outcomes, analysis of serum markers as predictive factors, and cardiac surveillance algorithm.	Burstein H, Harris L, et al. (2003). *Journal of Clinical Oncology*, 21 (15): 2889-95.
Chan 2006	Vinorelbine plus trastuzumab combination as first-line therapy for HER 2-positive metastatic breast cancer patients: an international phase II trial.	Chan A, Martin M, et al. (2006). *British Journal of Cancer*; 95: 788-93.
Jahanzeb 2002	Phase II trial of weekly vinorelbine and trastuzumab as first-line therapy in patients with HER2+ metastatic breast cancer.	Jahanzeb M, Mortimer J, et al. (2002). *The Oncologist* 7:410-7.

Bernardo 2004	Final results of phase II study of weekly trastuzumab and vinorelbine in chemonaive patients with HER2-overexpressing metastatic breast cancer [abstract].	Bernardo G, Palumbo R, et al. (2004). *Journal of Clinical Oncology*, 23: 59 (abstr 731).
De Wit 2004	Vinorelbine and trastuzumab as first line therapy in patients with HER2-positive metastatic breast cancer-interim analysis of a prospective, open-label, multicentre phase II trial [abstract].	DeWit M, Becker K, et al. (2004). *Ann Oncol,* 15 (suppl 3): 37 (abstr 138p).
Vinorelbine Alone		
Bruno 1995	Phase II trial of weekly i.v. vinorelbine as a single agent in first-line advanced breast cancer chemotherapy. The Latin-American experience.	Bruno S, Puerto VL, et al. (1995). *American Journal of Clinical Oncology* 18(5): 392-6.
Freyer 2003	Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy.	Freyer, G, Delozier T, et al. (2003). *Journal of Clinical Oncology*, 21(1): 35-40.
Fumoleau 1993	Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy.	Fumoleau P, Delgado F, et al. (1993). *Journal of Clinical Oncology,* 11(7): 1245-52.
Garcia-Conde 1994	Phase II trial of weekly IV vinorelbine in first-line advanced breast cancer chemotherapy.	Garcia-Conde J, Lluch A, et al. (1994). *Annals of Oncology* 5 (9): 854-7.
Romero 1994	Vinorelbine as first-line chemotherapy for metastatic breast carcinoma.	Romero A, Rabinovich M, et al. (1994). *Journal of Clinical Oncology,* 12(2): 336-41.
Vogel 1999	Vinorelbine as first-line chemotherapy for advanced breast cancer in women 60 years of age or older.	Vogel C, O'Rourke M, et al. (1999). *Annals of Oncology* 10(4): 397-402.

The studies published at the time of the review for the comparison of trastuzumab + vinorelbine versus vinorelbine alone in the second-line or subsequent setting were:

Trial ID	Protocol/ publication title	Publication citation
Trastuzumab + vinorelbine versus vinorelbine alone studies		
Comparative study		
Papaldo 2006	A phase II study on metastatic breast cancer patients treated with weekly vinorelbine with or without trastuzumab according to HER2 expression: changing the natural history of HER2-positive disease.	Papaldo P, Fabi A, et al. (2006). *Annals of Oncology,* 17: 630-6.
Trastuzumab + vinorelbine studies		
Non-comparative studies		
Bayo-Calero 2004	A multicenter study with trastuzumab and vinorelbine as first and 2nd line treatment in patients (pats) with Her2 positive metastatic breast cancer (MBC).	Bayo-Calero JL, Mayordomo-Ca´mara JI, et al. (2004). *Breast Cancer Res Treat*, 82 (Suppl 1) (Abstr 5069).
Burstein 2001	Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer.	Burstein, H. J., I. Kuter, et al. (2001). *Journal of Clinical Oncology* 19 (10): 2722-30.
Catania 2007	Optimizing clinical care of patients with metastatic breast cancer: a new oral vinorelbine plus	Catania C, Medici M, et al. (2007). *Annals of Oncology* 18 (12): 1969-

	trastuzumab combination.	75.
De Maio 2007	Vinorelbine plus 3-weekly trastuzumab in metastatic breast cancer: a single-centre phase 2 trial.	De Maio E, Pacilio C, et al. (2007). *BMC Cancer* 7: 50.
Suzuki 2003	Combination of trastuzumab and vinorelbine in metastatic breast cancer.	Suzuki Y, Tokuda Y, et al. (2003). *Japanese Journal of Clinical Oncology* 33(10): 514-7.
Vinorelbine studies		
Barni 1994	Vinorelbine as single agent in pretreated patients with advanced breast cancer.	Barni S, Ardizzoia A, et al. (1994). *Tumori* 80(4): 280-2.
Degardin 1994	Vinorelbine (navelbine) as a salvage treatment for advanced breast cancer.	Degardin M, Bonneterre J, et al. (1994). *Annals of Oncology* 5(5): 423-6.
Gasparini 1994	Vinorelbine is an active antiproliferative agent in pretreated advanced breast cancer patients: a phase II study.	Gasparini G, Caffo O, et al. (1994). *Journal of Clinical Oncology* 12 (10): 2094-101.
Ibrahim 1999	Phase II study of vinorelbine administered by 96-hour infusion in patients with advanced breast carcinoma.	Ibrahim N K, Rahman Z, et al. (1999). *Cancer* 86 (7): 1251-7.
Jara-Sanchez 2003	Vinorelbine as a 96-hour continuous infusion in heavily pretreated patients with metastatic breast cancer: a cooperative study by the GEICAM group.	Jara-Sanchez C, Martin M, et al. (2003). *Clinical Breast Cancer* 3 (6): 399-404.
Martin 2007	Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. [see comment].	Martin M, Ruiz A, et al. (2007). *Lancet Oncology* 8 (3): 219-25.
Nistico 2000	Weekly schedule of vinorelbine in pretreated breast cancer patients.	Nistico C, Garufi C, et al. (2000). *Breast Cancer Research & Treatment* 59 (3): 223-9.
Terenziani 1996	Vinorelbine: an active, non cross-resistant drug in advanced breast cancer. Results from a phase II study.	Tereziani M, Demicheli R, et al. (1996). *Breast Cancer Research and Treatment*, 39: 285-90.
Toussaint 1994	Phase I/II trial of continuous infusion vinorelbine for advanced breast cancer.	Toussaint C, Izzo M, et al. (1994). *Journal of Clinical Oncology*, 12 (10): 2102-12.
Udom 2000	Two weekly vinorelbine: administration in patients who have received at least two prior chemotherapy regimes for advanced breast cancer.	Udom DI, Vigushin DM, et al. (2000). *European Journal of Cancer*, 36: 177-82.
Verma 2007	Survival differences observed in metastatic breast cancer patients treated with capecitabine when compared with vinorelbine after pre-treatment with anthracycline and taxane.	Verma S, Wong SN, et al. (2007). *American Journal of Clinical Oncology*, 30 (3): 297-302.
Zelek 2001	Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma.	*Cancer*, 92 (9): 2267-72.

The studies published at the time of the review for the assessment of the use of trastuzumab as monotherapy were:

Trial ID	Protocol/ publication title	Publication citation
Comparative study (retrospective) – first, second and subsequent		
Trastuzumab versus trastuzumab + chemotherapy		
Kostler 2005	Single-agent trastuzumab versus trastuzumab plus cytotoxic chemotherapy in metastatic breast cancer: a single-institution experience.	Kostler WJ, Steger GG, et al. (2005). *Anti-Cancer Drugs,* 16 (2): 185-90.
Non-comparative studies – first-line treatment		
Vogel 2002	Efficacy and Safety of Trastuzumab as a Single Agent in First-Line Treatment of HER2-Overexpressing Metastatic Breast Cancer.	Vogel CL, Cobleigh MA, et al (2002). *Journal of Clinical Oncology,* 20 (3): 719-26.
Baselga 2005	Phase III Study of Efficacy, Safety and Pharmacokinetics of Trastuzumab Monotherapy Administered on a 3-weekly Schedule.	Baselga J, Carbonell X, et al. (2005). *Journal of Clinical Oncology,* 23 (10): 2162-70.
Non-comparative studies – second-/subsequent line treatment		
Cobleigh 1999	Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer that has Progressed after Chemotherapy for Metastatic Disease.	Cobleigh MA, Vogel MA, et al. (1999). *Journal of Clinical Oncology,* 117 (9): 2639-48.
Sawaki 2004	Efficacy and Safety of Trastuzumab as a Single Agent In Heavily Pre-treated Patients with Her2/NEU-Overexpressing Metastatic Breast Cancer.	Sawaki M, Ito Y, et al (2004). *Tumori,* 90: 40-3.

The studies published at the time of the review for the comparison of trastuzumab + capecitabine and capecitabine alone in the first-line setting were:

Trial ID	Protocol/ publication title	Publication citation
Trastuzumab + capecitabine studies		
Non comparative studies		
Yamamoto 2008	A phase II study of trastuzumab and capecitabine for patients with HER2-overexpressing metastatic breast cancer: Japan Breast Cancer Research Network (JBCRN) 00 Trial.	Yamamoto D, Iwase S, et al (2008). *Cancer Chemotherapy Pharmacology,* 61: 509-514.
Capecitabine studies		
Single arm of a randomised trial		
O'Shaughnessy 2001	Randomized, open-label, phase II trial of oral capecitabine (Xeloda®) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluoroucacil) as first-line therapy for advanced/metastatic breast cancer.	O'Shaughnessy J, Blum J, et al. (2001). *Annals of Oncology*, 12: 1247-1254.
Non comparative studies – first line		
Bajetta 2005	Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women.	Bajetta E, Procopio G, et al. (2005). *Journal of Clinical Oncology*, 23 (10): 2155-2161.

Minea 2004 (abstract only)	Capecitabine monotherapy for elderly patients with metastatic breast cancer.	Minea L, Stanculeanu D, et al (2004). *Journal of Clinical Oncology*, 22 (suppl 14): 76s
Yap 2007	Clinical efficacy of capecitabine as first-line chemotherapy in metastatic breast cancer – How low can you go?	Yap Y, Kendall A,, et al. (2007). *The Breast;* 16: 420-424.

The studies published at the time of the review for the comparison of trastuzumab + capecitabine and capecitabine alone in the second-line or subsequent settings were:

Trial ID	Protocol/ publication title	Publication citation
Trastuzumab + capecitabine versus capecitabine alone (beyond disease progression)		
Randomised trials		
von Minckwitz 2008	Capecitabine vs. capecitabine + trastuzumab in patients with HER-2 positive metastatic breast cancer progressing during trastuzumab treatment – the TBP phase III study (GBG 26 / BIG 3-05).	Von Minckwitz G, Zielinski C, et al. (2008). *44th ASCO Annual Meeting, May 30-June 3, Chicago, Illinois, USA.*

8. Results of Trials

Trastuzumab + taxane versus taxane alone:

The time to progression, progression free survival and overall survival across the direct randomised trials are presented in the table below.

	Median time in Months (95% CI)		Absolute difference	HR (95% CI)	P-value (log-rank)
Trial	**Trast + Taxane^**	**Taxane^**			
Time to disease progression[a]					
Slamon 2001*	N=92 6.9 (5.3, 9.9)	N=96 3.0 (2.1, 4.3)	**3.9**	NR	**<0.001**
Marty 2005	N=92 11.7 (9.2, 13.5)	N=94 6.1 (5.4, 7.2)	**5.6**	NR	**0.0001**
Gasparini 2006[a]	N=63 10.0	N=60 6.8	3.2	NR	0.076
Progression free survival					
Marty 2005	N=92 12.0 (9.9, 15.8)	N=94 6.8 (5.8, 8.3)	5.2	NR	0.1206
Overall survival					
Slamon 2001	N=92 22.1 (16.9, 30.7)	N=96 18.4 (12.7, 24.4)	3.7	NR	0.17
Marty 2005	N=92 31.3 (27.3, 42.0)	N=94 22.7 (19.1, 30.9)	8.6	NR	0.1449

Abbreviations: Trast=trastuzumab, HR=hazard ratio, NR=not reported

* primary outcome of the trial

^ paclitaxel in Slamon 2001 and Gasparini 2006, docetaxel in Marty 2005.

[a] reported as number of days in Gasparini, converted to months in this review: x days/30 = y months

Source: published reports of Slamon, Marty and Gasparini.

Note: Progression free survival was only reported for Marty 2005. Overall survival was not reported by Gasparini 2006.

There was a statistically significant increase in median time to disease progression in patients taking trastuzumab plus a taxane compared to taxane alone in the studies by Slamon and Marty, but not in the Gasparini trial.

The publication by Gasparini et. al. (2007) presented the results of an unplanned interim analysis of 123 patients after a median follow-up of 16.6 months. The planned sample size of the study was 160 patients, 80 in each treatment arm. In this study, HER2 positivity was only assessed using immunohistochemistry (IHC). There was no fluorescence in situ hybridisation (FISH) confirmation of HER2 positivity in IHC 2+ patients, which is standard practice. The primary endpoint of the study was overall response rate (ORR). The study was not powered to measure a statistically significant difference in time to progression, as this was a secondary endpoint. Overall survival results were not reported as median overall survival had not been reached. Although the difference in median time to progression between treatment arms did not reach statistical significance for the combined IHC 2+ and IHC 3+ population (p=0.076), there was a statistical difference in the IHC 3+ alone population and patients with visceral involvement (p=0.030).

The PBAC was concerned that the results for progression free survival in the Marty et al trial did not reach statistical significance, although it was the main trial used in the economic evaluation. The primary endpoint in Marty et al 2005 was overall response rate (best response). The study was not powered to measure a statistical difference between treatment arms for the secondary endpoints of time to progression (TTP), progression-free survival (PFS) and overall survival (OS). TTP was defined as the number of days from randomisation to date of documented progressive disease. PFS was defined as the number of days from randomisation to date of death or progressive disease.

The 24-month PFS results were not reported in the publication for Study M77001 but were provided in the accompanying 24-month Addendum on which the publication was based. At the 24-month data cut-off, all three endpoints (time to disease progression, progression-free survival and overall survival) were statistically significant different between the treatment arms of trastuzumab with a taxane versus a taxane alone.

Trastuzumab + aromatase inhibitor versus aromatase inhibitor alone:
Results from the TaNDEM trial indicated that a statistically significantly greater proportion of patients treated with combination trastuzumab and aromatase inhibitors achieved a partial and overall response, and also experienced increased time to progression and progression free survival, but not overall survival compared with those treated with aromatase inhibitors alone. There was no significant difference in overall survival, however more than half of the patients in the anastrozole-alone arm crossed over to a trastuzumab-containing regimen after progression of disease.

Trastuzumab + vinorelbine versus trastuzumab + taxane:
The time to progression and time to treatment failure for the randomised trial reported by Burstein 2007 are presented in the table below.

Outcome	Trast+vino N=41	Trast+taxane N=40	log rank p value
Time to progression	8.5 months	6.0 months	0.09
Time to treatment failure	5.8 months	4.7 months	0.15

Abbreviations: Trast-trastuzumab, Vino-vinorelbine

Data from Burstein (2007) indicated that the effectiveness of trastuzumab in combination with vinorelbine appeared to be similar as when it was combined with a taxane, as no significant differences in the outcomes reported were observed. In terms of safety, the

toxicity profiles of vinorelbine and taxanes differed. Vinorelbine appeared to be associated with more neutropenia (although treatment with filgrastim was not reported), whereas taxanes ware associated with alopecia (both taxanes) and fluid retention (docetaxel).

Trastuzumab monotherapy:
No information was presented in the review to inform the comparative effectiveness of trastuzumab monotherapy compared with trastuzumab + chemotherapy in either the first- or second-line setting. There was also no information presented in the review to inform the comparative safety of trastuzumab monotherapy compared with trastuzumab + chemotherapy in either the first- or second-line setting, however it would be anticipated that any adverse events that are attributable to the chemotherapy would not be experienced by patients being treated with trastuzumab monotherapy.

Data from Kostler (2005) indicated that trastuzumab monotherapy may have similar effectiveness to trastuzumab + chemotherapy, however these data needed to be considered carefully as the study was retrospective and very few patients treated with monotherapy were included in the analysis (n=14).

A greater proportion of patients treated with trastuzumab experienced cardiac dysfunction compared to patients treated with chemotherapy alone. Current practice was aimed at avoiding cardiovascular events by application of cardiovascular eligibility criteria and prospective cardiac monitoring. The costs for this monitoring were included in the economic evaluation.

For PBAC's views see Recommendation and reasons.

9. Clinical Claim

For PBAC's views see Recommendation and reasons.

10. Economic Analysis

Premodelling studies:
The following premodelling studies were undertaken:

- Estimation of the administration schedules of the therapies of interest used in Australian clinical practice;
- Use of premedications for the various therapies;
- Monitoring associated with the treatment of metastatic breast cancer;
- Extrapolation of trial data to a 10-year time horizon:
  - Exponential extrapolation of trial data used in the AUC model, with a hazard ratio = 1 beyond truncation;
  - Weibull function(s) for the extrapolation of trial data used in the Markov model. Time-dependent transition probabilities were estimated from the extrapolation.

Two economic evaluations, an Area Under the Curve (AUC) and a Markov model, comparing the costs and outcomes if trastuzumab was available on the PBS for patients with HER2 positive metastatic breast cancer with the costs and outcomes if trastuzumab was not available were presented. Both models had a time horizon of 10 years and both estimated an incremental cost per life year gained and a cost per Quality Adjusted Life Year (QALY). The AUC model was constructed for consistency purposes with the previous model considered by the PBAC in the earlier submissions.

Results from two trials were used to derive outcomes for both models: the M77001 trial (reported by Marty 2005) and the TaNDEM trial. The M77001 trial compared trastuzumab + docetaxel with docetaxel alone in patients with metastatic breast cancer. The TaNDEM trial compared trastuzumab + anastrozole with anastrozole alone.

The incremental cost/ extra life-year gained over 10 years using the AUC model was between $75,000 and $105,000, and the incremental cost/ extra QALY gained over 10 years was between $105,000 and $200,000.

For the Markov model, the incremental discounted cost/extra discounted life-year gained over 10 years was between $75,000 and $105,000. The incremental discounted cost/extra discounted QALY gained over 10 years was between $105,000 and $200,000.

Sensitivity analysis showed that the models were most sensitive to the estimate of treatment effect for trastuzumab (AUC), utility weights applied to patients in the "progressing" disease state in both models and the cost of trastuzumab (demonstrated by increasing the assumed weight of patients in both models). Sensitivity analyses for the AUC model were conducted during the review.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year were estimated to be less than 10,000, and was based on the number currently receiving trastuzumab through the Herceptin Program. The annual expenditure on the Herceptin Program was currently between $30 million and $60 million (excluding GST).

12. Recommendation and Reasons

The Government had requested the PBAC to review the clinical and cost-effectiveness of trastuzumab when used in the treatment of HER-2 positive metastatic breast cancer (MBC). Since 2002 trastuzumab has been publicly funded for use in metastatic breast cancer in a program that operates independent of the Pharmaceutical Benefits Scheme.

The Committee considered that, in terms of clinical effectiveness:

- Combined therapy with trastuzumab plus taxanes (docetaxel or paclitaxel) was more effective, but associated with greater toxicity, than taxanes alone as a first line treatment for MBC. This had previously been accepted by the PBAC;
- Dual therapy involving trastuzumab plus aromatase inhibitors in oestrogen receptor positive patients was more effective, but associated with greater toxicity, than aromatase inhibitors alone in first and second line MBC;
- There appeared to be a trend of increased efficacy of trastuzumab plus vinorelbine over vinorelbine alone for first-line treatment of MBC, but this was based on a comparison of single arm studies with confounding;
- Treatment with trastuzumab plus vinorelbine was equi-effective with trastuzumab plus taxanes for first-line treatment of MBC. The toxicity profiles of vinorelbine and taxanes differed. Vinorelbine appeared to be associated with more neutropenia (although treatment with filgrastim was not reported), whereas taxanes were associated with hair loss and fluid retention;
- The additional benefit of 'triple therapy' involving trastuzumab plus taxane plus another cytotoxic agent (e.g. carboplatin or capecitabine) was uncertain and was more toxic; and

- The effectiveness of trastuzumab used beyond disease progression was uncertain with some studies reporting decreasing time to progression and response rates with subsequent treatment, whereas others reported comparable time to progression and response rates over time.

The Committee further agreed that:

- The evidence of clinical benefit for trastuzumab when used as monotherapy was uncertain;
- The evidence of clinical benefit for trastuzumab when it was used for the first time as part of second or third line treatment in patients who have been pre-treated with one or more lines of chemotherapy is inconclusive; and
- There was no information on the efficacy of trastuzumab in patients with MBC who also received trastuzumab as part of their adjuvant treatment.

The Committee considered that the Markov model used to assess the cost-effectiveness of trastuzumab in MBC was robust. Any assumptions that might favour trastuzumab and underestimate the incremental cost-effectiveness ratio (ICER), for example: that there was no use of drug beyond progression and that there were no costs associated with progression; were likely to be balanced by assumptions that bias the ICER against trastuzumab, for example the likelihood that the survival advantage in first line setting was underestimated because of cross over and the poor patient selection resulting from inaccurate testing for HER-2 when some of the studies were designed.

However, at the current price of trastuzumab the base case incremental cost effectiveness ratio was above the range usually considered by the PBAC as being acceptable for PBS-subsidy lying between $105,000 and $200,000 (assuming a section 100 listing, including wastage and assigning a utility of 0.65 for the progressing disease health state). Even if, as considered not unreasonable by PBAC, the utility for progressing disease was set at 0.7, the ICER remained unacceptably high lying between $75,000 and $105,000. (The Committee also noted that the use of trastuzumab in combination with vinorelbine was not supported by the TGA registration for trastuzumab and therefore that the above cost-effectiveness analysis which assumed 40 % use of this regimen may not represent the most appropriate base case. The incremental cost-effectiveness ratio in a "TGA approved indication" analysis was between $105,000 and $200,000).

The PBAC noted the high base case ICER (lying between $105,000 and $200,000) for trastuzumab for HER-2 positive MBC and considered that a significant price reduction would be required in order for the ICER to fall into a range which would make it acceptable for PBS-subsidy, and asked that the Minister be so advised. The Committee further requested the Minister be advised that the PBAC in this instance may be prepared to consider a full economic evaluation of trastuzumab capturing all stages of the disease.

Lastly the Committee asked that the Minister be advised that, although the measures listed below would not by themselves make trastuzumab acceptably cost-effective in terms of PBS-subsidy, they would nonetheless substantially improve the cost-effectiveness of trastuzumab when supplied via the non-PBS Herceptin program (and these same measures would be stipulated by PBAC in the event of a PBS-subsidy of trastuzumab in MBC):

- confine trastuzumab use to first line treatment of MBC in combination with a taxane (docetaxel or paclitaxel). The use of trastuzumab as first line treatment of MBC in

combination with vinorelbine was supported by the clinical trial evidence, but this combination was not registered with the TGA;

- confine use of trastuzumab to patients who have their HER-2 positive status confirmed by ISH testing;
- allow trastuzumab to be used once only for MBC. Changing the partner chemotherapy should only be permitted if patients develop an intolerance to the chemotherapy agent and not as a means of continuing treatment with trastuzumab beyond disease progression;
- not allow trastuzumab to be used as monotherapy in patients newly diagnosed with HER-2 positive MBC (noting that around one-third of the current usage of Herceptin on the non-PBS MBC program is as monotherapy); unless there was an absolute contraindication to chemotherapy.
- not allow trastuzumab to be used as part of triple combination therapy;
- not allow trastuzumab to be used beyond progression (of MBC);
- not allow use in combination with aromatase inhibitors;

The PBAC indicated its willingness to continue to work with the Government and the sponsor on any of the matters raised in this review.

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 has no further comment.