7.5 PERTUZUMAB, 420 mg/14 mL injection, 1 x 14 mL vial; Perjeta®; Roche Products Pty Ltd.

TRASTUZUMAB, 150 mg injection, 1 × 150 mg vial, 60 mg injection, 1 × 60 mg vial; Herceptin®, Roche Products Pty Ltd.

7.8 TRASTUZUMAB EMTANSINE, 100 mg injection, 1 x 100 mg vial, 160 mg injection, 1 x 160 mg vial; Kadcyla®, Roche Products Pty Ltd.

1 Purpose of application

1.1 Section 100 listing for trastuzumab for treatment of a patient with HER2+ metastatic breast cancer (MBC) who has not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The previous submissions were considered in September 2000, December 2000, September 2001 and November 2008.

1.2 Section 100 listing for trastuzumab for treatment of a patient with HER2+ metastatic breast cancer whose disease has progressed despite prior treatment with trastuzumab for metastatic disease. This is the first submission for this listing.

1.3 Section 100 listing for pertuzumab in combination with trastuzumab and docetaxel for treatment of a patient with HER2+ metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease and have a performance status of 0 – 1. The first submission was considered in March 2014.

1.4 Section 100 listing for trastuzumab emtansine (T-DM1) for treatment of a patient with HER2+ metastatic breast cancer who has received prior treatment with trastuzumab and a taxane and whose disease has progressed despite treatment with trastuzumab for metastatic disease. The previous submissions were considered in July 2013 and in March 2014.

2 Requested listings

Requested listing for trastuzumab

Name, manner of administration, form and strength	Maximum amount (mg)	No. of repeats	Proprietary name and manufacturer	
First-line MBC				
Initial dose				
TRASTUZUMAB 150 MG INJECTION, 1 × 150 MG VIAL TRASTUZUMAB 60 MG INJECTION, 1 × 60 MG VIAL	1000	0	HERCEPTIN	Roche Products Pty Limited
Continuing doses				
TRASTUZUMAB 150 MG INJECTION, 1 × 150 MG VIAL TRASTUZUMAB 60 MG INJECTION, 1 × 60 MG VIAL	750	3	HERCEPTIN	Roche Products Pty Limited
Second and later-lines MBC				
Initial dose				
TRASTUZUMAB 150 MG INJECTION, 1 × 150 MG VIAL TRASTUZUMAB 60 MG INJECTION, 1 × 60 MG VIAL	1000	0	HERCEPTIN	Roche Products Pty Limited
Continuing doses				
TRASTUZUMAB 150 MG INJECTION, 1 × 150 MG VIAL TRASTUZUMAB 60 MG INJECTION, 1 × 60 MG VIAL	750	3	HERCEPTIN	Roche Products Pty Limited

Requested listing for pertuzumab

Name, manner of administration, form and strength	Maximum amount (mg)	No. of repeats	Proprietary name and manufacturer	
Initial dose				Roche Products Pty Limited
Pertuzumab 420 mg injection, 2 × 420 mg vial	840	0	PERJETA	
Continuing doses				
Pertuzumab 420 mg injection, 1 × 420 mg vial	420	3	PERJETA	

Requested listing for T-DM1

Name, manner of administration, form and strength	Maximum amount (mg)	No. of repeats	Proprietary name and manufacturer	
Trastuzumab emtansine 100 mg injection, 1 × 100 mg vial	450	8	KADCYLA	Roche Products Pty Limited
Trastuzumab emtansine 160 mg injection, 1 × 160 mg vial				

For more detail on PBAC's view, see section 7 and 8 "PBAC outcome"

3 Background

3.1 TGA status: Trastuzumab was TGA registered on 14 September 2000 for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2: a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease, b) in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

3.2 Pertuzumab was TGA approved on 6 May 2013, in combination with trastuzumab and docetaxel, for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease.

3.3 T-DM1 was TGA approved on 3 September 2013 for the treatment of patients with HER2-positive metastatic (Stage IV) breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.

3.4 Previous considerations: Trastuzumab was previously considered by PBAC in 2000, 2001, and in November 2008 for the first-line treatment of HER2+ metastatic breast cancer (MBC). Trastuzumab in second and later-lines has not been previously considered by PBAC. Pertuzumab (used in combination with trastuzumab and a taxane) was previously considered by PBAC in March 2014. T-DM1 was previously considered by PBAC in July 2013 and in March 2014.

3.5 The key differences between the previous submission and current resubmission in terms of trastuzumab are summarised below. The differences for pertuzumab and T-DM1 are that drug prices, mark-ups and fees have been updated (with flow-on effects to the ICER and financial costs). Also the efficacy of pertuzumab had been further quantified with the reporting of the median overall survival of patients in the pertuzumab arm of the Cleopatra study.

Summary of the previous submission and current resubmission for trastuzumab

	Submissions considered in March 2014	Current resubmission
Trastuzumab first-line and later lines		
Requested restriction	The intention was to maintain the Herceptin Program as is and for trastuzumab used in combination with pertuzumab to be accessed via the PBS. …in combination with pertuzumab and docetaxel for patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.	Proposed PBS listing signifies an end to the Herceptin Program and for all use of trastuzumab currently funded via the Herceptin Program to be moved to the PBS. Proposed authority required listing requests separate PBS restrictions for first-line and second- and later-line treatment. HER2-positive metastatic breast cancer • First-line: Clinical criteria: Patients must not have received prior trastuzumab for metastatic disease • Second- and later-lines: Clinical criteria: Patients whose disease has progressed despite treatment

	Submissions considered in March 2014	Current resubmission
		with trastuzumab for metastatic disease The clinical criteria in both restrictions include: HER2 positivity must be demonstrated by in situ hybridisation (ISH) either in the primary tumour or a metastatic lesion. A grandfather clause is also proposed: A patient who commenced treatment with trastuzumab for HER2-positive metastatic breast cancer prior to (listing date) and who continues to receive treatment at the time of application will be eligible for PBS-subsidised treatment.
Trastuzumab first-line		
Requested price (DPMA)	For initial dose: [redacted] (public hospital); [redacted] (private hospital). For continuing dose: [redacted] (public hospital); [redacted] (private hospital).	Initial dose: [redacted] (public hospital); [redacted] (private hospital). Continuing dose: [redacted] (public hospital); [redacted] (private hospital).
Economic evaluation	ICER = $45,000-$75,000/QALY [redacted] • Exponential extrapolation with same probability of death in both arms • No discounting • Exclusion of CT scans • Exclusion of mark-ups and dispensing fees	ICER = $45,000-$75,000/QALY [redacted] • Log-logistic extrapolation (best fit) with same probability of death in both arms • Annual discounting of health outcomes and costs at 5% per year. • Inclusion of CT scans. • The inclusion of mark-ups and dispensing fees • The prices of carboplatin, docetaxel, paclitaxel and vinorelbine are updated (price disclosure-related reductions from 1 April 2014 and 1 October 2014) • The updating of all PBS fees as of 1 July 2014
Extent of use and financial implications	More than $100 million over 5 years	More than $100 million over 5 years.
[redacted]	[redacted]	[redacted]
Trastuzumab later lines		
Requested price (DPMA)	Not included	Initial dose: [redacted] (public hospital); [redacted] (private hospital). Continuing dose: [redacted] (public hospital); [redacted] (private hospital).
Clinical evidence	Not included	An open label, phase III RCT comparing trastuzumab + capecitabine versus capecitabine alone as second-line treatment in patients with HER2+ MBC (n=156): the GBG 26 trial. A retrospective observational study by Berghoff et al. (2013), comparing overall survival (OS) of HER2+ MBC patients (n=201) who received several lines of trastuzumab therapy (n=115), a single-line of therapy (n=58), and a control group (n=28).
Economic evaluation	Not included	Two economic models: GBG 26: ICER = $105,000-$200,000/QALYG; Berghoff et al. (2013): ICER = $45,000-$75,000/LYG. A cost comparison to lapatinib + capecitabine is also

	Submissions considered in March 2014	Current resubmission
		presented. The incremental savings per patient are [redacted].
Extent of use and financial implications	Not included	$60-$100 million over 5 years.
[redacted] s	[redacted].	[redacted]

Source: Compiled during the evaluation

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Clinical place for the proposed therapy

4.1 The resubmission proposed a change to the clinical management algorithm as follows: use of trastuzumab in first and later-line treatment, pertuzumab in first-line treatment in combination with trastuzumab + docetaxel and T-DM1 in second-line treatment of HER2+ MBC.

4.2 The Metastatic Breast Cancer Stakeholder Meeting (May 2014) minutes (http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-stakeholder-meetings/metastatic-breast-cancer-stakeholder-meeting-may-2014.pdf) stated 'clinicians considered that for a majority of patients not already on trastuzumab treatment, the following drug treatment regimens setting aside individual patient circumstances, in order of line of treatment, are likely to be prescribed:

- 1st-line treatment: pertuzumab (+ trastuzumab + taxane)
- 2nd-line treatment: trastuzumab emtansine monotherapy
- 3rd-line treatment and later: lapatinib + capecitabine or trastuzumab + chemotherapy'.

4.3 DUSC considered that insufficient consideration has been given to the use of trastuzumab monotherapy in the current treatment algorithm. The Pre-Sub-Committee Response (PSCR) argued that trastuzumab monotherapy is infrequently used according to a clinical survey and is not recommended by relevant guidelines. DUSC noted the definition of monotherapy is inconsistent across settings. Trastuzumab monotherapy is defined in the following way:

- trastuzumab – no chemotherapy, no aromatase inhibitors (AIs)
- trastuzumab – no chemotherapy, no endocrine therapies (including AIs)
- trastuzumab – no chemotherapy, AIs not mentioned.

It is not clear what definition of trastuzumab monotherapy was used in the clinical survey.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 Trastuzumab first-line: The resubmission did not propose a comparator for trastuzumab for first-line therapy. In the 2008 PBAC trastuzumab review, the comparators accepted by the PBAC were placebo or the following chemotherapy regimens alone (those that are commonly co-administered with trastuzumab): taxanes (with or w/o other chemotherapy), aromatase inhibitors, vinorelbine (PBAC Ratified Minutes November 2008). The resubmission presented direct clinical evidence and cost-effectiveness estimates against docetaxel alone only.

5.2 Trastuzumab second- and later-lines: The resubmission did not propose a comparator for trastuzumab for second- and later-line therapy.

5.3 Pertuzumab: trastuzumab + taxane. PBAC previously considered this the appropriate comparator.

5.4 T-DM1: lapatinib + capecitabine. The current clinical treatment algorithm in the resubmission suggested that, currently in the second-line setting, 40% receive lapatinib + capecitabine, 58% receive trastuzumab + chemotherapy and 2% receive trastuzumab monotherapy. Reflecting this, the first submission for T-DM1 proposed a mixed comparator; however the PBAC considered at the July 2013 and March 2014 meeting that lapatinib + capecitabine alone to be the most appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (4), health care professionals (5) and organisations (1) via the Consumer Comments facility on the PBS website relating to pertuzumab. The comments described a range of benefits of treatment with pertuzumab including the ability to live a healthy and active life with minimal impact from continuing treatment, prolonging survival and increasing quality of life.

6.3 The PBAC noted and welcomed the input from individuals (9), health care professionals (9) and organisations (1) via the Consumer Comments facility on the PBS website relating to trastuzumab emtansine. The comments described a range of benefits of treatment with trastuzumab emtansine including improvements in quality of life, reduced side effects and improved prognosis.

6.4 Consumer comments in relation to all three treatments note the financial stress that is experienced by families when paying for these treatments privately.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical trials

6.5 The resubmission was based on four head-to-head trials:

- M77001: trastuzumab + docetaxel vs docetaxel (n=188). This trial was the same as the previous submission for trastuzumab.
- GBG26: trastuzumab + capecitabine to capecitabine (n=156). This trial was included in the previous submission for T-DM1.
- CLEOPATRA: pertuzumab + trastuzumab + docetaxel vs trastuzumab + docetaxel (n=808). This trial was the same as the previous submission. In the PSCR, the sponsor provided an update on the results for overall survival in the CLEOPATRA study.
- EMILIA: T-DM1 vs lapatinib + capecitabine (n=991).

The resubmission presented Berghoff (2013): an observational study comparing multiple-line and single-line treatment with trastuzumab to no treatment with trastuzumab (n=201).

6.6 Details of the trials presented in the resubmission are provided in the table below.

Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
Pertuzumab		
CLEOPATRA (NCT00567190)	Clinical Study Report – WO20698/TOC4129g: A phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer. Research Report No. 1046288.	October 2011
	Updated Clinical Study Report – WO20698/TOC4129g - A phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer – Report No. 1053649. Internal study report title.	December 2012
	Swain SM, Ewer MS, Cortes J, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: A randomized, double-blind, placebo-controlled phase III study.	Oncologist 2013;18(3):257-264.
	Swain SM, Im Y-H, Im S-A et al. Safety of pertuzumab (P) with trastuzumab (T) and docetaxel (D) in patients (pts) from Asia with HER2-positive metastatic breast cancer (MBC): Results from the phase III trial CLEOPATRA.	Cancer Res 2013a;73(24 Suppl): Poster Abstract P4-12-10.
	Baselga J, Cortés, J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.	New England Journal of Medicine 2012;366(2):109-119.
	Baselga J, Cortes J, Im SA et al. Biomarker analysis in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC).	Cancer Research 2012;72(24):Suppl.3. Abstract S5-1.
	Baselga J & Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer.	Clinical Breast Cancer 2010;10(6):489-491.

Trial ID	Protocol title/ Publication title	Publication citation
T-DM1		
EMILIA (NCT00829166)	Clinical Study Report - TDM4370g (BO21977) - EMILIA. A randomized, multicenter, phase III open- label study of the efficacy and safety of T-DM1 vs. capecitabine + lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy. Report No. 1044311.	August 2012.
	Blackwell K.L. Miles D. Gianni L. Krop I.E. Welslau M. Baselga J. Pegram M.D. Oh D.-Y. Dieras V. Olsen S.R. Fang L. Lu M.W. Guardino E. Verma S. Primary results from EMILIA, a phase III study of T-DM1 (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane.	J Clin Oncol 2012; 30:18 SUPPL. 1.
	Pegram M.D. Blackwell K. Miles D. Bianchi G.V. Krop I.E. Welslau M. Baselga J. Oh D.-Y. Dieras V. Guardino E. Olsen S.R. Fang L. Lu M. Verma S. Primary results from EMILIA, a phase III study of T-DM1 (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane.	J Clin Oncol 2012; 30:27 SUPPL.
	Verma S, Miles D et al. Updated overall survival results from EMILIA, a phase 3 study of T-DM1 (T-DM1) vs. capecitabine and lapatinib in HER2-positive locally advanced or metastatic breast cancer.	Presentation at ESMO 2012 Congress; Vienna, Austria.
	Verma S, Dieras V et al. EMILIA: A phase III, randomized, multicenter study of trastuzumab-DM1 (T-DM1) compared with lapatinib (L) plus capecitabine (X) in patients with HER2-positive locally advanced or metastatic breast cancer (MBC) and previously treated with a trastuzumab-based regimen.	J Clin Oncol 2011;29 (suppl; abstr TPS116). ASCO Annual Meeting, 2011.
	Verma S. Miles D. Gianni L. Krop I.E. Welslau M. Baselga J. Pegram M. Oh D.-Y. Dieras V. Guardino E. Fang L. Lu M.W. Olsen S. Blackwell K. T-DM1 for HER2-positive advanced breast cancer.	New England Journal of Medicine 2012; 367(19):1783-1791.
	Wang B. Jin J. Wada R. Fang L. Lu D. Guardino E. Swain S.M. Untch M. Girish S. Exposure-efficacy relationship of T-DM1 (T-DM1) in EMILIA, a phase III study of T-DM1 versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC).	J Clin Oncol 2013; 31:15 SUPPL. 1.
	Wang B. Jin J. Wada R. Fang L. Saad O. Olsen S. Althaus B. Swain S. Untch M. Girish S.Pharmacokinetics and exposure-efficacy relationship of T-DM1 in EMILIA, a phase 3 study of T-DM1 vs capecitabine and lapatinib in HER2-positive locally advanced or metastatic breast cancer.	Cancer Research 2012; 72:24 SUPPL. 3.
	Welslau M, Diéras V et al. Patient-reported outcomes from EMILIA, a phase 3 study of T-DM1 (T-DM1) vs. capecitabine and lapatinib (XL) in HER2-positive locally advanced or MBC. Poster presentation 329P.	ESMO 2012 Congress; Vienna, Austria.
	Welslau M, Dieras V, Sohn JH et al. Patient-reported outcomes from EMILIA, a randomized phase 3 study of trastuzumab emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer.	Cancer. 2014;120(5):642-51.

Trial ID	Protocol title/ Publication title	Publication citation
	Krop I, Lin N, Blackwell K et al. Efficacy and safety of trastuzumab emtansine (T-DM1) vs lapatinib plus capecitabine (XL) in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) and central nervous system (CNS) metastases: Results from a retrospective exploratory analysis of EMILIA.	Cancer Res 2013;73(24 Suppl): Poster Abstract P4-12-27.
Trastuzumab		
M77001	Clinical Study Report –M77001. A multicenter, randomized comparative study on the efficacy and safety of Herceptin (trastuzumab) plus docetaxel versus docetaxel alone as first line treatment in patients with HER2-positive metastatic breast cancer. Report No. 1011941.	September 2003.
	Marty M, Cognetti F, Maraninchi D. Randomised phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2 positive metastatic breast cancer administered at first line treatment (the M77001 study group).	J Clin Oncol. 2005;23:4265-74.
GBG 26 (NCT00148876)	Clinical Study Report – GBG 26. A multicenter randomized phase III study to compare capecitabine alone or in combination with trastuzumab in patients with HER2-positive metastatic breast cancer and progression after previous treatment with trastuzumab (treatment beyond progression, TBP). German Breast Group.	September 11, 2008.
	von Minckwitz G, du Bois A, Schmidt M et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: A German Breast Group 26/ Breast International Group 03-05 Study.	J Clin Oncol 2009;27(12):1999-2006.
	von Minckwitz G, Schwedler K, Schmidt M, et al. Final overall survival analysis of the TBP phase III study (GBG 26/BIG 3-05): Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment.	Cancer Res 2010;70(24 Suppl 2):Abstract P6-14-05.
	von Minckwitz G, Zielinski C, Maartense E et al. 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).	Annals of Oncology 2008;19 (Suppl 8):viii63-76. Abstract 133O.
	von Minckwitz G, Zielinski C, Maartense E et al. 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).	Journal of Clinical Oncology 2008;26 (May 20 Suppl; Abstract 1025).
	von Minckwitz G, Schwedler K, Schmidt M et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer.	European Journal of Cancer 2011;47(15):2273-2281.

Source: Table B.2.2, pp 6-7, Section B of the resubmission.

6.7 The key features of the direct randomised trials and the observational study are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
T-DM1 vs lapatinib + capecitabine						
EMILIA	991	R, OL 12.65 months for PFS and 18.85 months for OS	Low	HER2+ LABC/MBC. Had received prior trastuzumab. Progression during/after recent treatment for LABC/MBC or within 6 months after completing adjuvant therapy (fast-relapsing patients)	PFS and OS	Used
Pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel						
CLEOPATRA	808	R, DB 29.7 months for pertuzumab arm and 30.1 months for placebo	Low	HER2+ (IHC3+ or FISH ≥2.0) first-line MBC or locally recurrent unresectable breast cancer and had not received chemotherapy or biologic therapy for their metastatic disease. ECOG performance status of 0 or 1. LVEF ≥ 50%. No disease progression within 12 months after neoadjuvant or adjuvant therapy	PFS, OS; ORR, Duration of objective response and Time to symptom progression (QoL)	Used
Trastuzumab + capecitabine vs capecitabine alone						
GBG 26	156	OL, R, MC	Medium	LVEF ≥50%, Karnofsky performance status evaluation ≥60%, IHC3+ or FISH+, LABC or MBC not suitable for surgery or radiotherapy alone. Trastuzumab treatment given previously for at least ≥12 weeks, treatment free interval of trastuzumab for a maximum of 6 weeks). No more than one chemotherapy for palliation.	TTP, OS, clinic benefit, duration of response, ORR	Used
Trastuzumab + docetaxel vs docetaxel alone						
M77001	186	OL, R, MC	Low	LVEF > 50%, ECOG performance status ≤2, life expectancy ≥12 weeks, no previous chemotherapy except for neoadjuvant or adjuvant treatment, HER2+ IHC 3+ assessed by HercepTest and/or FISH+	ORR, OS, PFS, TTP	Used
Trastuzumab +/- chemotherapy						
Berghoff et al (2013)	201	Observational study	High	HER2+ MBC patients treated between 1999 and 2009 who received at least one line of trastuzumab, HercepTest of 3+ or FISH, historical control arm patients who never received trastuzumab treatment, LVEF > 50%	OS, TTP	Used

DB=double blind; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; MC=multi-centre; OL=open label; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; R=randomised; TTP=time to progression.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative effectiveness

6.8 Trastuzumab first-line: based on M77001, trastuzumab + docetaxel were associated with a longer time to progression (TTP) and overall survival (OS) compared to docetaxel alone. The results for TTP were statistically significant, but OS was not statistically significant.

6.9 Trastuzumab second-line: based on GBG 26, trastuzumab + capecitabine were associated with longer TTP and OS compared to capecitabine alone. The results for TTP were statistically significant, but OS was not statistically significant. The ESC noted that the GBG 26 trial is of poor methodological quality and was terminated early after low recruitment.

6.10 Trastuzumab multiple-lines: based on Berghoff (2013), an observational study, trastuzumab (multiple-lines) and trastuzumab (single-line) were associated with longer OS compared to the historical control group (no trastuzumab). The OS results were statistically significant. The ESC noted that Berghoff (2013) was a retrospective observational study and is likely to be subject to bias and confounding. The effect size may be overestimated because of the use of a historical control group, which is likely to be subject to other differences in clinical practice (apart from the availability of trastuzumab).

6.11 Pertuzumab: based on CLEOPATRA, pertuzumab + trastuzumab + docetaxel were associated with statistically significantly longer progression free survival (PFS) and OS compared to trastuzumab + docetaxel. The comparative effectiveness claim is unchanged from previous submission. The ESC noted the updated OS result (11 February 2014 cut-off) from the CLEOPATRA trial presented in the PSCR.

6.12 T-DM1: based on EMILIA, T-DM1 was associated with statistically significantly longer PFS and OS compared to lapatinib + capecitabine. The comparative effectiveness claim is unchanged from the previous resubmission.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative harms

6.13 Trastuzumab first-line: based on M77001, the addition of trastuzumab was associated with higher incidence of: serious adverse events (SAEs), grade 3 and grade 4 AEs; but with lower risk of AEs leading to withdrawal from treatment. The comparative harms are unchanged from the previous submission.

6.14 Trastuzumab second-line: based on GBG 26, the addition of trastuzumab was associated with lower incidence of: SAEs and AEs leading to discontinuation of treatment. The risk of grade 3 AEs and deaths was similar in both treatment arms.

6.15 Pertuzumab: based on CLEOPATRA, the addition of pertuzumab was associated with higher incidence of: serious AEs, AEs leading to dose interruption or modification; and slightly higher incidence of: grade 3 and 4 AEs; and AEs leading to discontinuation of treatment. The comparative harms are unchanged from the previous submission.

6.16 T-DM1: based on EMILIA, T-DM1, compared to lapatinib + capecitabine, was associated with fewer: any AEs; treatment related grade≥3 AEs; all grade≥3 AEs; SAEs; treatment discontinuations; and deaths. The comparative harms are unchanged from the previous submission.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Benefits/harms

6.17 A summary of the comparative benefits and harms for the drugs under consideration and the comparators is presented in the table below.

Trastuzumab

Benefit/harm summary (M77001)

Outcome	N	HRR or RR (95%CI)	Median months		Increment
			Trastuzumab + docetaxel	Docetaxel	
Benefits					
TTP	188	0.50 (0.24, 1.06)	11.7*	6.1*	5.6
OS	188	[redacted]	31.2	22.7*	8.5
Harms					
SAEs, n (%)	186	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 AEs, n (%)	186	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to discontinuation, n (%)	186	[redacted]	[redacted]	[redacted]	[redacted]

T+D=trastuzumab + docetaxel; D=docetaxel; HRR=hazard rate ratio; OS=overall survival; TTP=time to progression. Note: HRR for TTP = 0.50 (0.24, 1.06) using $\ln(0.5)/TTP_{T+D}$ / $(\ln(0.5)/TTP_{D})$ (from results reported in Marty et al (2005)). * The TTP and OS results were reported in Marty (2005) (estimated by Kaplan-Meier). CSR M77001 results were reported in FAS (full analysis set) population (Table 20, p60 of the CSR M77001). Sources Table B.2.4 Section B of the resubmission; Marty et al (2005) pp 4267-4268; compiled during evaluation.

Benefit/harm summary (GBG 26)

Outcome	N	HRR or RR (95%CI)	Trastuzumab + capecitabine	Capecitabine	Increment
Benefits					
TTP (median months, 95% CI)	156	0.69 [redacted]	8.2 (7.25, 11.212)	5.6 (4.16, 6.3)	2.6
OS (median months, 95% CI)	156	0.76 [redacted]	25.5 (19.02, 30.69)	20.4 (17.77, 24.66)	5.1
Harms					
SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to discontinuation, n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SAE: serious adverse events; AE: adverse events; HRR: hazard rate ratio. Source: Table B.6.4 and Table B.6.6 Section B of the commentary and compiled during evaluation.

Benefit/harm summary (Berghoff 2013)

Outcome	N	HR	Trastuzumab (multiple-lines)	Trastuzumab (single-line)	Control	Increment
Benefits						
OS (median months, 95% CI)	201		47 (40.46, 53.54)	28 (22.95, 33.05)	13 (6.79, 19.21)	na
OS (median months, 95% CI)	201	0.317	41 (34.57, 47.43)		13 (6.79, 19.21)	28
Harms						
Symptomatic heart failure, n	201	na	1		0	na
Treatment related deaths, n	201	na	0		0	na

SAE: serious adverse events; AE: adverse events; HRR: hazard rate ratio. Source: Table B.6.5 and Table B.6.6 Section B of the commentary and compiled during evaluation.

Pertuzumab

Benefit/harm summary (CLEOPATRA)

Outcome	N	HRR or RR (95%CI)	Median months (95% CI)		Increment
			Pertuzumab + trastuzumab +docetaxel	Trastuzumab + docetaxel	
Benefits					
PFS(median months, 95% CI) (May 2012 cut-off)	808	0.69 (0.58, 0.81)	18.7 (17, 22)	12.4 (10, 14)	6.3
OS (median months, 95% CI) (May 2012 cut-off)	808	0.66 (0.52, 0.84)	Not reached (42, -)	37.6 (34, -)	N/A
OS (median months, 95% CI) (Feb 2014 cut-off)	808	0.68 (0.56, 0.84)	56.5	40.8	15.7
Harms					
Grade 3/4 events, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs (SAE), %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SAE: serious adverse events; AE: adverse events; HRR: hazard rate ratio. Source: Table B.6.1 and Table B.6.6 Section B of the commentary and compiled during evaluation.

T-DM1

Benefit/harm summary (EMILIA)

Outcome	N	HR or RR (95%CI)	Median months (95% CI) [d]		Increment
			T-DM1	Lapatinib + capecitabine	
Benefits					
PFS (months) (Jan 2012)	991	0.65 (0.59, 0.77)	9.6 [redacted]	6.4 [redacted]	3.2
OS (months) (Jul 2012)	991	0.68 (0.55, 0.85)	30.9 [redacted]	25.1 [redacted]	5.8
Harms					
Grade 3/4 events	978	[redacted]	200 (41%)	278 (57%)	-16%
Serious AEs (SAE)	978	[redacted]	76 (16%)	88 (18%)	-2%
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SAE: serious adverse events; AE: adverse events; HRR: hazard rate ratio. Source: Table B.6.2 and Table B.6.6 Section B of the commentary and compiled during evaluation.

6.18 Trastuzumab first-line: on the basis of head-to-head trial ITT analyses, the comparison of trastuzumab + docetaxel and docetaxel resulted in a median of: approximately 5.6 months difference in PFS and 8.5 months difference in OS (data cut off at 6 months after last patient enrolled).

6.19 Trastuzumab second and later-lines: on the basis of head-to-head trial ITT analyses, the comparison of trastuzumab + capecitabine and capecitabine resulted in a median of: approximately 2.6 months difference in TTP and 5.1 months difference in OS (median follow up 15.6 months). On the basis of a retrospective study, the comparison of trastuzumab alone in multiple-lines and trastuzumab alone in single-line resulted in a median of approximately 28 months difference in OS.

6.20 Pertuzumab: on the basis of head-to-head trial ITT analyses, the comparison of pertuzumab + trastuzumab + docetaxel and trastuzumab + docetaxel resulted in a median of: approximately 6.3 months difference in PFS (05/12 data cut off) and 15.7 months difference in median OS (02/14 data cuff off).

6.21 T-DM1: on the basis of head-to-head trial ITT analyses, the comparison of T-DM1 and lapatinib + capecitabine resulted in a median of: approximately 3.2 months difference in PFS (01/12 data cut off) and 5.8 months difference in OS (07/12 data cut off).

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical claim

6.22 Trastuzumab first-line: the resubmission made no new claims with regards to trastuzumab in first-line therapy with respect to efficacy and safety. However, PBAC has previously accepted the following claims (PBAC Ratified Minutes, trastuzumab, 2008):

- combined therapy with trastuzumab plus taxanes (docetaxel or paclitaxel) is more effective, but associated with greater toxicity, than taxanes alone as a first-line treatment for MBC;
- dual therapy involving trastuzumab plus aromatase inhibitors in oestrogen receptor positive patients is more effective, but associated with greater toxicity, than aromatase inhibitors alone in first and second-line MBC;
- there appears to be a trend of increased efficacy of trastuzumab plus vinorelbine over vinorelbine alone for first-line treatment of MBC, but this is based on a comparison of single arm studies with confounding; and
- treatment with trastuzumab plus vinorelbine is equi-effective with trastuzumab plus taxanes for first-line treatment of MBC. The toxicity profiles of vinorelbine and taxanes differ. Vinorelbine appears to be associated with more neutropenia (although treatment with filgrastim was not reported), whereas taxanes are associated with hair loss and fluid retention.

6.23 Trastuzumab second- and later-lines: the resubmission described trastuzumab as superior in terms of response rates, PFS and OS in patients who have continued trastuzumab after disease progression compared with those who have not, and the safety profile in later-line therapy is comparable to the trastuzumab and lapatinib arms of GBG-26 and EGF100151 (Cameron 2010) (treatment in second-line). The

ESC noted that no safety data is provided and that this clinical claim has not previously been considered by the PBAC.

6.24 The magnitude of any superiority of trastuzumab in the second-line setting over other treatments is unclear given:

- no direct-RCT evidence was provided of efficacy of trastuzumab as monotherapy or with concomitant chemotherapies, as occurs in clinical practice, other than capecitabine
- early stopping and cross-over to trastuzumab therapy in trial GBG-26 confounds the overall survival results for the combination with capecitabine
- Berghoff (2013) is a retrospective historical-controlled observational study and is likely to be subject to bias and confounding
- the resubmission did not propose a comparator for trastuzumab for second- and later-lines of therapy.

6.25 The PBAC accepted the view in the pre-PBAC response that it is now unlikely that robust evidence will be added to the existing evidence base for use of trastuzumab in metastatic breast cancer settings other than first-line therapy.

6.26 Pertuzumab first-line: the previous submission described pertuzumab, when used in combination with trastuzumab plus docetaxel, as superior in terms of comparative effectiveness and "slightly worse" in terms of comparative safety over trastuzumab plus docetaxel alone. This was previously considered by PBAC as reasonable.

6.27 T-DM1 second-line: the previous resubmission described T-DM1 as superior in terms of comparative effectiveness and superior in terms of comparative safety over lapatinib plus capecitabine. In March 2014, the PBAC accepted this clinical claim, although noted that some of the toxicity profile of T-DM1 was less favourable than that of its comparator.

6.28 The ESC noted that the evidence used to support the claim of superiority for T-DM1 in the second-line setting may not be appropriate given the new treatment algorithm would result in this being used after most people progress on a combination of pertuzumab + trastuzumab + taxane, whereas the patients in the key T-DM1 study had to progress on trastuzumab + taxane. Therefore the efficacy of T-DM1 in patients who progress on a pertuzumab combination therapy is unknown. The pre-PBAC response stated that, in the EMILIA trial, 8.7% of L+C and 10.3% of T-DM1 patients received prior pertuzumab. Test-for-interaction analysis also shows that there is no statistically significant difference between patients pre-treated with pertuzumab and those not (p = 0.3578, stratified).

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

6.29 Trastuzumab first-line: the structure of the economic evaluation remained unchanged from the previous submission. The key differences to the inputs are described in the table below.

6.30 Trastuzumab second-line: a new 'Area under the curve (AUC)' model was presented. Patients were assumed to be in one of three mutually exclusive health states: PFS (within which patients may be responders/non-responders), progressive disease (PD) and death. Two treatment options were considered: six chemotherapies (capecitabine, nab-paclitaxel, vinorelbine, paclitaxel, docetaxel and doxorubicin) with trastuzumab, and without trastuzumab.

6.31 For trastuzumab second-line, the magnitudes of the effect size on TTP and OS may be unreliable as they were based on the GBG-26 trial, which the ESC considered to be of poor methodological quality and was terminated early after low recruitment.

Summary of model structure and rationale for trastuzumab second-line

Time horizon	7 years in the model base case versus 15.6 months in trial
Outcomes	Mean time in PFS (years) and in progression (years), life years and QALYs
Methods used to generate results	An AUC analysis with three health states: PFS, PD and death.
Cycle length	1 week, with a half-cycle correction.
Transition probabilities	Kaplan-Meier estimates of PFS and OS are used up to 15.56 months; PFS was extrapolated using log-normal and OS using log-logistic.
Discount rate	5% for costs and outcomes
Software	Excel 2010

Source: compiled during the evaluation

6.32 Trastuzumab in multiple MBC lines: a new AUC model was presented. Patients were assumed to be in one of two health states - survival (OS) or death. Two treatment options were considered: trastuzumab and no trastuzumab.

6.33 The ESC considered that the results from the 'trastuzumab in multiple lines' model are likely to favour trastuzumab due to:

- the design of Berghoff (2013), specifically with respect to the historical 'control' group (pre-availability of trastuzumab), which is:
  - unlikely to be applicable to current Australian practice because of differences in concomitant therapies over time; and
  - likely to result in an overestimate of survival advantage attributable directly to trastuzumab (Berghoff 2013);
- the results for 'trastuzumab multiple-lines' were presented as $45,000-$75,000/LYG. The ESC noted that additional analysis by the evaluator calculated the ICER to be between $105,000-$200,000/QALYs;
- the exclusion of costs and disutilities associated with adverse events (AEs), the costs of other chemotherapies, and the cost of HER2 re-testing.

6.34 Pertuzumab and T-DM1: the structure of the economic evaluation remained unchanged from the previous submission. The only differences for pertuzumab and T-DM1 were that drug prices, mark-ups and fees have been updated (with flow-on effects to the ICER and financial costs).

6.35 **Key drivers of the model for trastuzumab first and second-line**

Description	Method/Value	Impact
Trastuzumab first-line		
Cross-over adjustment	RPSFT adjustment	High, favours trastuzumab
Cost of AEs	Not included	High, favours trastuzumab
Utility values	Utility value for progression being 0.55	Low, favours trastuzumab
HER2 testing	Not included	Low, favours trastuzumab
Trastuzumab second-line		
Clinical data	Clinical data based on GBG 26.	High, favours trastuzumab
Utility values	Utility values are taken from Lloyd (2006) that are relating to first-line treatment only.	High, favours trastuzumab
HER2 testing	Not included	Low, favours trastuzumab
Cost of AEs	Not included	Low, favours trastuzumab

Source: compiled during the evaluation

Key drivers of the model for trastuzumab multiple-lines

Description	Method/Value	Impact
Clinical data	Clinical data based on Berghoff 2013.	High, favours trastuzumab
Health outcomes	Results reported in terms of life years gained.	High, favours trastuzumab
HER2 testing	Not included	Low, favours trastuzumab
Disutilities and cost of AEs	Not included	Low, favours trastuzumab
Costs of other chemotherapies	Not included	Unclear

Source: compiled during the evaluation

6.36 The ESC considered drug prices were a key driver in the models and resulted in a high ICER in all lines of therapy.

6.37 The ESC considered that the resubmission did not address PBAC's concerns regarding post-progression costs in the economic models presented for pertuzumab, T-DM1, trastuzumab first-line or second-line.

6.38 **Results of the economic evaluations presented in the resubmission**

Component	Trastuzumab not available	Trastuzumab available	Increment
Trastuzumab first-line (with [redacted] price discount for trastuzumab)			
Mean total cost over 10 years	[redacted]	[redacted]	[redacted]
Mean life years over 10 years	[redacted]	[redacted]	[redacted]
Mean QALY over 10 years	[redacted]	[redacted]	[redacted]
Incremental cost per LYG over 10 years			[redacted]
Incremental cost per QALYG over 10 years			[redacted]
Trastuzumab second-line (with [redacted] price discount for trastuzumab)			
Mean total cost over 7 years	[redacted]	[redacted]	[redacted]
Mean life years over 7 years	[redacted]	[redacted]	[redacted]
Mean QALY over 7 years	[redacted]	[redacted]	[redacted]
Incremental cost per LYG over 7 years			[redacted]
Incremental cost per QALYG over 7 years			[redacted]
Trastuzumab multiple-lines (with [redacted] price discount for trastuzumab first-line and [redacted] discount for trastuzumab second and later-lines)			
Mean total cost over patient lifetime	[redacted]	[redacted]	[redacted]
Mean life years over patient lifetime	[redacted]	[redacted]	[redacted]
Incremental cost per LYG over 7 years			[redacted]
	Pertuzumab + trastuzumab + docetaxel	**Trastuzumab + docetaxel**	**Increment**
Pertuzumab			
Mean total cost over 10 years	[redacted]	[redacted]	[redacted]
Mean QALY over 10 years	[redacted]	[redacted]	[redacted]
Incremental cost per QALYG over 10 years			[redacted]
	T-DM1	**Lapatinib + capecitabine**	**Increment**
T-DM1			
Mean total cost over 10 years	[redacted]	[redacted]	[redacted]
Mean QALY over 10 years	[redacted]	[redacted]	[redacted]
Incremental cost per QALYG over 10 years			[redacted]

Source: Table D.5.1, Table D.5.4 and Table D.5.7 of the commentary *and Pertuzumab Economic Evaluation.xls and T-DM1 Economic Evaluation.xls*

The redacted table above shows:
Incremental cost per QALYG over 10 years for trastuzumab first line to be between $45,000-$75,000;
Incremental cost per QALYG over 7 years for trastuzumab second line to be between $105,000-$200,000;
Incremental cost per LYG over 7 years for trastuzumab multiple lines to be between $45,000-$75,000;
Incremental cost per QALYG over 10 years for pertuzumab to be between $45,000-$75,000;
Incremental cost per QALYG over 10 years for T-DM1 to be between $45,000-$75,000;

6.39 Trastuzumab first-line: the results of the economic evaluation were uncertain due to the adjustments for cross-over, the application of 0.7 as the utility for progression, the exclusion of costs and disutilities associated with AEs, and the exclusion of post-progression costs. The PSCR argued that the application of 0.7 as the utility for

progression was appropriate and considered 'not unreasonable' in the 2008 PBAC review. This value was assumed to be representative of patients having further treatment options upon progression. The PSCR also noted that the lower utility applied for the progression health state in both second-line models is estimated using Lloyd's algorithm and was deemed representative for patients with limited further treatment options.

6.40 Trastuzumab second-line: the results of the economic model were uncertain due to the clinical evidence, based on GBG-26, which is of low reliability. Furthermore additional uncertainty arises from: the application of utility values from Lloyd (2006) and the omission of diminishing quality of life over time; the omission of AE-related costs; the omission of HER2 re-testing; the lack of sensitivity analysis around the extrapolation methods; and the exclusion of post-progression costs. The PSCR argued that it is appropriate and best practice to exclude post-progression drug costs in health-economic evaluations as they are all, by definition of being PBS listed, considered cost-effective. The PSCR acknowledged that longer survival may increase expenditure post progression which is addressed by the greater later-line discount and [redacted], hence the PSCR argued that the majority of expected expenditure to Government for the MBC algorithm is cost-effective and known with certainty The ESC considered that this was a major issue as the costs should have been included, however their importance in the context of the broader decision is unclear.

6.41 Trastuzumab multiple-lines: it is likely that the ICER of trastuzumab multiple-lines was underestimated. There were likely biases in the clinical evidence (Berghoff 2013), and the results were not translated to QALYs gained. The PSCR acknowledged the limitations in the Berghoff data, but argued that the results are consistent with other ICERs for trastuzumab, pertuzumab and T-DM1 in first-line treatment. The PBAC noted the additional comments provided in the pre-PBAC response in relation to the Berghoff 2013 study, and concluded that whilst the study might represent the best available evidence for later-line use of trastuzumab, residual concerns remain about bias and confounding reducing confidence in its results.

6.42 Furthermore, the resubmission did not include the cost and disutilities associated with AEs, the costs of other chemotherapies, and the cost of HER2 re-testing. The PSCR argued that exclusion of adverse events in the economic model did not affect the magnitude or certainty of the results, as they were not drivers of the economic evaluation. The PSCR also argued that most SAEs are related to concomitant therapy rather than trastuzumab, and therefore as chemotherapies are the same in both treatment arms, these would cancel out, while the inclusion of cardiac events was not warranted because of the small absolute numbers and small QOL impact. The ESC disagreed with the PSCR and considered that exclusion of adverse events was inappropriate.

6.43 Finally, Berghoff (2013) did not report the concomitant chemotherapies administered with trastuzumab (or the extent of monotherapy use), and so the applicability of Berghoff (2013) is unknown.

6.44 The ESC considered that the increment of 2.64 years to be large. This was considered to be highly optimistic, as it was based on retrospective observational data with an historical control for the no trastuzumab group. The incremental survival

benefit was therefore likely to be overestimated. The ESC considered that the applicability to the Australian setting was unclear.

6.45 Pertuzumab: the PBAC previously considered the pertuzumab economic model to be reasonably reliable despite various issues (especially post-progression costs) and the potential for the ICER to be underestimated. The ICER for pertuzumab presented in the resubmission was of $45,000-$75,000/QALY. An update of the economic evaluation incorporating the final analysis of data from CLEOPATRA and a broad taxane restriction was presented in the PSCR, generating an ICER of $45,000-$75,000/QALY gained.

6.46 T-DM1: the PBAC noted that the TDM-1 model and ICER had not changed from the previous submission.

6.47 The table below summarises the results of the sensitivity analysis presented in the resubmission.

Results of sensitivity analysis

	Incremental cost	QALYG	ICER
Base-case	[redacted]	[redacted]	[redacted]
Earliest time point of cross-over in the RPSFT model to estimate the OS of the docetaxel arm in M77001	[redacted]	[redacted]	[redacted]
Latest time point of cross-over in the RPSFT model to estimate the OS of the docetaxel arm in M77001	[redacted]	[redacted]	[redacted]
Different probability of death in log-logistic extrapolation of OS	[redacted]	[redacted]	[redacted]

Source: Table D.1.5, p10 and Table D.1.6, p11 of section D of the resubmission.

6.48 The table below summarises the results of additional sensitivity analysis conducted during the evaluation.

Results of the additional analyses conducted during the evaluation

	Incremental cost	QALYG	ICER
Trastuzumab first-line			
Base-case	[redacted]	[redacted]	[redacted]
ITT (no RPSFT adjustment)	[redacted]	[redacted]	[redacted]
Utility associated with "free of progression" = [redacted] for trastuzumab + docetaxel, and [redacted] for docetaxel alone*	[redacted]	[redacted]	[redacted]
Utility associated with progressive disease = [redacted]	[redacted]	[redacted]	[redacted]
[redacted] price discount for trastuzumab	[redacted]	[redacted]	[redacted]
Trastuzumab second-line			
Base-case	[redacted]	[redacted]	[redacted]
[redacted] price discount for trastuzumab later-lines	[redacted]	[redacted]	[redacted]
[redacted] price discount for trastuzumab later-lines	[redacted]	[redacted]	[redacted]
Trastuzumab multiple-lines			
Base case	[redacted]	[redacted]	[redacted]
Convert LYG to QALYs using [redacted]	[redacted]	[redacted]	[redacted]

6.49 The ESC noted that the resubmission inconsistently applied utilities across the models. For example, the models for trastuzumab first-line and pertuzumab applied a utility of 0.7 in the post-progression health state (applied until death), but the models for trastuzumab second-line and T-DM1 applied utilities of 0.781 and 0.817 in the

pre-progression state, and 0.555 in the post-progression health state (applied until death). Costs and disutilities due to associated with adverse events were not included in all models.

6.50 The PSCR argued that applying a single utility weight of 0.555 to survival inappropriately favours the comparator and overestimates the ICER for trastuzumab, failing to account for the time where patients are in the progression-free health state. The ESC acknowledged this argument, but stated that this is unlikely to give a realistic estimate of the ICER. By definition, patients would have progressed from first-line therapy to become eligible for later-line use.

6.51 The resubmission also provided a cost-analysis of trastuzumab ± chemotherapy vs. lapatinib + capecitabine and claimed that it would be informative to benchmark the discount offered for trastuzumab in second and later MBC lines to the only PBS-listed HER2-blocking agent in this setting.

Results of the economic evaluations

Cost item (per patient)	Lapatinib + capecitabine	Trastuzumab (with [redacted] discount) ± chemotherapy
Drug costs		
Trastuzumab	[redacted]	[redacted]
Lapatinib	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Doxorubicin (pegylated liposomal)	[redacted]	[redacted]
Nab-paclitaxel	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
Administration costs		
Cost of IV administration	[redacted]	[redacted]
Total cost of treatment per patient	[redacted]	[redacted]

Source: Table D.3.1, p24 of section D of the resubmission

For more detail on PBAC's view, see section 7 "PBAC outcome"

Estimated PBS usage & financial implications

6.52 The HER2+ MBC Stakeholder Meeting (25 May 2014) noted that:

- patients tend to remain on HER2 blockade (either trastuzumab or lapatinib) from the time of diagnosis to the end of their life unless placed on palliative care;
- determining the length of time that patients receive trastuzumab treatment is difficult due to the lack of this data collection; and
- determining the number of patients who receive one continuous course of treatment from those who remained on extended treatment or those who receive multiple courses and chemotherapy partners is difficult due to the absence of appropriate data collection.

6.53 The following estimates of PBS usage and financial implications were presented in the resubmission.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Pertuzumab in first-line					
Number treated pertuzumab					
Trastuzumab in first-line					
Number treated trastuzumab with pertuzumab first-line					
Number treated trastuzumab without pertuzumab in first-line					
T-DM1 in second-line					
Number treated T-DM1					
T-DM1 in third-line					
Number treated T-DM1					
Trastuzumab in third-line and later-lines					
Number treated trastuzumab					
Estimated net cost to PBS/MBS					
Pertuzumab in first-line					
Pertuzumab - net cost to PBS					
Pertuzumab, trastuzumab and docetaxel - net cost to MBS					
Trastuzumab in first-line					
Trastuzumab with pertuzumab - net cost to PBS					
Trastuzumab without pertuzumab - net cost to PBS					
T-DM1 in second-line					
T-DM1 second-line - net cost to PBS					
T-DM1 second-line - net cost to MBS					
T-DM1 in third-line					
T-DM1 second-line - net cost to PBS					
T-DM1 second-line - net cost to MBS					
Trastuzumab in third-line and later-line					
Trastuzumab third- and later-line - net cost to PBS					
Trastuzumab third- and later-line - net cost to MBS					
Estimated total net cost in first-line - net cost PBS/MBS					
Estimated total net cost in second-line - net cost PBS/MBS					
Estimated total net cost in third-line and later-line - net cost PBS/MBS					

The redacted table above shows:
Estimated total net cost in first-line - net cost PBS/MBS to be $30-$60 million per year;
Estimated total net cost in second-line - net cost PBS/MBS to be $10-$20 million per year in the first year and $20-$30 million per year in subsequent years;
Estimated total net cost in third-line and later-line - net cost PBS/MBS to be $20-$30 million per year in years 1-3 and $10-$20 million per year in years 4 and 5.

6.54 The PSCR stated that "a broad taxane restriction with a higher uptake for pertuzumab, 95% up from 83%, was considered in the sensitivity analyses in the resubmission and these corresponding financial estimates now form the base-case for proposed [redacted] for pertuzumab".

6.55 DUSC considered the estimates to be underestimated. The main issues were:

- the uptake of pertuzumab is likely to be higher than estimated. Given the substantial survival benefit in the CLEOPATRA trial, uptake may be close to 100%.
- the financial estimates may not adequately account for increased prevalence of HER2+ metastatic breast cancer. Due to the survival gains from the newer treatments, there is likely to be a much larger pool of patients eligible for third-line trastuzumab in the future. It is assumed the quantity of trastuzumab used for third-line treatment will not increase. However, it is not known whether this would increase use of trastuzumab in later lines of therapy. A risk share arrangement limiting trastuzumab expenditure to current levels of expenditure would minimise financial risk to Government.
- the financial estimates include cost-offsets for reductions in the use of paclitaxel and nab-paclitaxel. It is unlikely the listing of pertuzumab for first-line therapy will substantially change the currently administered cytotoxic chemotherapy.

6.56 DUSC revised the base case estimates with the following changes:

- increase the uptake of pertuzumab from 83% to 95%, and
- co-administered chemotherapy to remain the same as the current situation (55.3% docetaxel, 22.53% paclitaxel and 22.14% nab-paclitaxel).

Revised estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
First-line					
Pertuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second-line					
T-DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Third + lines					
T-DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall Net cost to the PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to Government for MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to State and Territory Health Budgets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Savings to Government from Termination of Herceptin Program	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost to Government less savings from Herceptin Program	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The redacted table above shows the total cost to the PBS to be $60-$100 million per year in years 1 – 5.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Quality Use of Medicines

6.57 DUSC considered a main issue to be that the listing of trastuzumab for second- and later-line treatment may promote the use of trastuzumab until death, exposing patients to treatment-related adverse events where there is little evidence of benefit from continued treatment.

Financial Management – Risk Sharing Arrangements

[redacted]

7 PBAC Outcomes

7.1 The PBAC recommended the listing of pertuzumab under Section 100 (Efficient Funding of Chemotherapy Drugs Program) for the treatment of HER2 positive metastatic breast cancer in combination with trastuzumab and a taxane in the first-line setting.

7.2 The PBAC recommended extending the listing of trastuzumab under Section 100 (Efficient Funding of Chemotherapy Drugs Program) for the treatment of HER2 positive metastatic breast cancer in the first-line setting as well as in patients whose disease has progressed despite treatment with trastuzumab for metastatic disease. The PBAC recommended that implementation of this recommendation should be implemented alongside the cessation of the Herceptin program. The PBAC reiterated its March 2014 view, in response to the sponsor's assurance, that the reduced prices offered for trastuzumab should not be reversed with the advent of a subcutaneous formulation.

7.3 The PBAC decided to defer its decision on trastuzumab emtansine (T-DM1), noting uncertainties in the economic model by omitting post-progression costs, the nature of the treatment effect and the place of T-DM1 once pertuzumab is available. The PBAC noted the clinical need for T-DM1, however emphasised the limitations in the applicability of the evidence in the key trial given that patients had progressed on trastuzumab + taxane rather than pertuzumab + trastuzumab + taxane as is most likely to occur in clinical practice.

7.4 The PBAC summarised the key differences in the resubmission from those presented at its March 2014 consideration as follows:

- the price reduction offered for trastuzumab was extended from [redacted] for its first-line use and from [redacted] for its second-line use
- the risk-share arrangement was extended to provide greater budget certainty by [redacted] across all HER2 blockers provided by the sponsor, with a [redacted] rebate beyond these caps

7.5 The PBAC noted that no changes were made to the prices for pertuzumab or T-DM1 or to the ICER for T-DM1.

7.6 The PBAC noted the stakeholder meeting following the deferral of pertuzumab and TDM-1. The meeting clarified the clinician and patient view on current and future treatment of mBC in Australia.

7.7 The PBAC noted strong support for the listing of trastuzumab, pertuzumab and T-DM1 received through the Consumer Comments facility expressing a range of benefits of treatment including improving quality of life and survival.

7.8 The PBAC noted that the evidence on comparative harms was unchanged from the most recent previous submissions for trastuzumab first-line, pertuzumab and T-DM1, but noted that, for trastuzumab later-line, there was a lower incidence of serious adverse effects and adverse effects leading to discontinuation compared to capecitabine alone.

Trastuzumab

7.9 The PBAC considered that trastuzumab is likely to be used both as monotherapy and with chemotherapy, noting DUSC advice that the definition of monotherapy is inconsistent and unclear (see Section 4 above).

7.10 The PBAC considered that HER2 blockade is being used until death, with and without continuous chemotherapy, for a significant number of patients, which not only affects treatment costs, but also exposes patients to treatment-related adverse events despite there being limited evidence of benefit from continued treatment.

7.11 The PBAC reaffirmed its previous comments on the Herceptin program – specifically that for 14 years this program has provided an effective drug to patients with HER2 positive metastatic breast cancer at very high ICERs (approximately $100,000/QALY for first-line use and close to $300,000/QALY for later-line use). The PBAC noted that the cost to government was greatly in excess of predicted costs for the Herceptin program. The Herceptin program has in some instances served as a barrier to adoption of best practice evidence-based prescribing. For example the Herceptin program does not support the use of trastuzumab with non-taxane chemotherapy partners (eg vinorelbine, capecitabine).

7.12 The PBAC further noted that supplying trastuzumab on the PBS for all patients with metastatic breast cancer would remove the need for the Herceptin program, and compared with this status quo, would support evidence-based clinical practice, ensure patient equity, and improve the cost-effectiveness of the drug. PBS listing would also simplify its accessibility as a necessary partner for pertuzumab in an even more effective combination under arrangements that would make such combination use more acceptably cost-effective (in the range of $45,000/QALY to $75,000/QALY).

7.13 The PBAC noted that no comparators were proposed for trastuzumab in first or later lines of therapy.

7.14 The PBAC noted clinical data showing trastuzumab + docetaxel compared to docetaxel alone (trial M77001 – previously submitted trial) in the first-line setting resulted in a median progression free survival of 5.6 months and overall survival of 8.5 months, while in the later-line setting in combination with capecitabine compared to capecitabine alone (GBG26 – new trial) offered an improved time-to-progression of 2.6 months and median overall survival of 5.1 months. The PBAC noted that the resubmission presented a new observational study comparing multiple-lines and single-line treatment with trastuzumab compared to no treatment with trastuzumab (Berghoff 2013). The retrospective observational study design is likely to be subject to bias and confounding. The effect size of 28 months for overall survival is likely to be overestimated because of the historical control groups, favouring trastuzumab. However, the PBAC noted that the claim of superiority of trastuzumab over other treatments in the second-line setting is not well supported, given the available evidence and that trastuzumab has been available in clinical practice for a long time.

7.15 The PBAC noted that the ICER for first-line use of trastuzumab remains high (around $45,000-$75,000/QALY) but more certain, and very high ($105,000-$200,000/QALY)

and less certain for second-line use. The PBAC accepted that there was no possibility of further data being collected to address these uncertainties.

7.16 The PBAC considered that the ICER of trastuzumab across multiple-lines ($45,000-$75,000/LYG) was likely to be underestimated. This is due to the likely biases in the clinical evidence, not translating the results into QALYs gained, excluding the costs and disutilities associated with adverse effects, excluding costs of other chemotherapies and excluding the cost of HER2 re-testing.

7.17 Given these ICERs despite the reduced effective prices of trastuzumab being offered, the opportunity to discontinue the Herceptin program with all its disadvantages was an important consideration for the PBAC when deciding to recommend trastuzumab as requested.

Pertuzumab

7.18 The PBAC noted that the comparator for pertuzumab was trastuzumab + taxane, and that this comparator had previously been accepted by the PBAC. The PBAC noted that the PSCR presented updated results for overall survival from the pertuzumab + trastuzumab + docetaxel vs trastuzumab + docetaxel trial (CLEOPATRA).

7.19 The PBAC noted the CLEOPATRA trial showed that pertuzumab + trastuzumab + docetaxel offers additional clinical benefit compared with trastuzumab + docetaxel (incremental gains of 15.7 months in median overall survival as updated and of 6.3 months in median progression-free survival). This is a substantial overall survival gain, particularly in the metastatic setting.

7.20 The economic model for pertuzumab was unchanged from the previous submission. The PBAC previously considered the model to be reasonably reliable. The PBAC noted the ICER varied between $45,000-$75,000/QALY (submission) and $45,000-$75,000/QALY (final analysis of data from CLEOPATRA and modifying to a broad taxane restriction). The PBAC noted that the latter ICER included 22.14% use of nab-paclitaxel, but rejected this because the increased cost of nab-paclitaxel, at more than 30 times the cost of paclitaxel, which had price reductions due to PBS reforms, means that nab-paclitaxel should be excluded from use with pertuzumab + trastuzumab by the pertuzumab restriction. However, overall, the PBAC considered the cost-effectiveness of pertuzumab to be acceptable given the survival benefits seen.

7.21 The PBAC noted DUSC advice which highlighted that uptake of pertuzumab is likely to be higher than estimated due to the substantial survival benefits, and that due to these survival gains, there is also likely to be a larger prevalent pool of patients eligible for later lines of treatment in the future. The PBAC noted DUSC's revised estimates, but reiterated that under the restriction for pertuzumab, use of nab-paclitaxel as a co-administered taxane would be excluded.

7.22 The PBAC considered that the risk share arrangement for pertuzumab (and T-DM1 if subsequently recommended) would offer a degree of budget certainty, including in relation to the use of this drug beyond disease progression. [redacted]

[redacted]The PBAC noted that the cost of pertuzumab and trastuzumab are higher in the first year of listing due to an estimated 150 grandfathered patients transitioning to PBS-listed treatment.

7.23 The Committee recommended that the Department negotiate a Risk Share Arrangement [redacted]

Trastuzumab emtansine (T-DM1)

7.24 The PBAC noted that the comparator for T-DM1 was lapatinib + capecitabine, and that this comparator had previously been accepted by the PBAC. The PBAC also noted that the clinical data submitted for T-DM1 (EMILIA) was the same as in previous submissions.

7.25 By comparison with CLEOPATRA for pertuzumab, the PBAC noted the EMILIA trial showed unequivocal, but less substantial, additional clinical benefit for T-DM1 compared with lapatinib + capecitabine (incremental gains of 5.8 months in median overall survival and of 3.2 months in median progression-free survival).

7.26 The PBAC recalled that, at its March 2014 meeting, the Committee considered the T-DM1 economic model to be reasonably reliable. However, the PBAC again noted:

- the total modelled LYG of [redacted] (of which [redacted] years is progression-free and [redacted] years is in progression)
- this means that [redacted] of the modelled overall survival improvement is in progression
- there was a [redacted] greater use of HER2 therapy ([redacted] vs [redacted]) following progression in the T-DM1 arm compared with lapatinib + capecitabine – of note was that [redacted] of patients in T-DM1 arm had lapatinib compared to only [redacted] in the lapatinib + capecitabine arm
- the model did not account for extra post-progression costs beyond the first-line post-progression treatment. The inclusion of first-line post-progression costs incorrectly makes the ICER for T-DM1 appear favourable. In the comparator arm (lapatinib + capecitabine) the first exposure to post-progression treatment will be with T-DM1 (which is more expensive than lapatinib + capecitabine), while lapatinib + capecitabine will be used after progression in the T-DM1 arm. These post-progression costs continue to mount despite incremental benefits falling.

7.27 The PBAC noted the projected costs to the PBS for T-DM1 of more than $100 million over the first three years of listing were greater than those projected for the more effective pertuzumab over the time period and then similar to those projected for pertuzumab. This is due to T-DM1 being used in both second and third line patients in the first three years of listing.

7.28 The PBAC considered that there is a clinical place for T-DM1, but was concerned by the issues around the use in clinical practice and the applicability of the evidence. Namely, the PBAC was concerned that, in that the key T-DM1 trial, patients had progressed on trastuzumab + taxane and not pertuzumab + trastuzumab + taxane as would occur in clinical practice once pertuzumab is listed. The PBAC noted the use of pertuzumab in the EMILIA trial, but considered that the number of patients in the trial was too small to substantiate this claim and the treatment effect of T-DM1 in patients who have progressed following pertuzumab + trastuzumab is not yet known.

7.29 Overall, the PBAC considered that a T-DM1 price generating an ICER between $45,000-$75,000/QALY by the model as presented would likely address the uncertainty related to the issues identified above.

Consequential considerations

7.30 The PBAC noted that its recommended restrictions for both pertuzumab and trastuzumab are complex, with one course of pertuzumab to be subsidised per patient lifetime. It was noted that the restrictions should reflect current evidence and legitimise clinical practice by allowing use of trastuzumab beyond progression and a range of partner chemotherapy options, with the exception of nab-paclitaxel. The PBAC noted that the restrictions should ensure that patients currently accessing trastuzumab on the Herceptin program would continue to have access trastuzumab through the PBS. The finalised restrictions for trastuzumab and pertuzumab would also have flow-on consequences for the lapatinib restriction.

7.31 The PBAC advised that pertuzumab and trastuzumab are not suitable for prescribing by nurse practitioners.

7.32 The PBAC recommended that the Safety Net 20 Day Rule should not apply to pertuzumab or trastuzumab.

Outcome:
Recommended (pertuzumab and trastuzumab)
Deferred (trastuzumab emtansine)

Subsequent to the meeting, the sponsor presented a pricing proposal for trastuzumab emtansine which was considered by the PBAC out of session.

[redacted]

The PBAC recommended the listing of trastuzumab emtansine under Section 100 (Efficient Funding of Chemotherapy Drugs Program) for treatment of a patient with HER2 positive metastatic breast cancer who has received prior treatment with trastuzumab and a taxane and whose disease has progressed despite treatment with trastuzumab for metastatic disease.

The Committee reiterated that the Department negotiate a Risk Share Arrangement [redacted]

The PBAC noted that its recommended restriction for trastuzumab emtansine is complex, with one course of trastuzumab emtansine to be subsidised per patient lifetime. The finalised restrictions for trastuzumab emtansine would also have flow-on consequences for the lapatinib restriction.

The PBAC advised that trastuzumab emtansine is not suitable for prescribing by nurse practitioners.

The PBAC recommended that the Safety Net 20 Day Rule should not apply to trastuzumab emtansine.

Advice to the Minister under subsection 101(3BA) of the Act
In accordance with subsection 101(3BA) of the Act, the PBAC advised that it is of the opinion that trastuzumab should not be treated as interchangeable on an individual patient basis with other therapies for HER2 positive metastatic breast cancer. In accordance with subsection 101(3BA) of the Act, the PBAC advised that it is of the opinion that pertuzumab should not be treated as interchangeable on an individual patient basis with other therapies for HER2 positive metastatic breast cancer. In accordance with subsection 101(3BA) of the Act, the PBAC advised that it is of the opinion that trastuzumab emtansine should not be treated as interchangeable on an individual patient basis with other therapies for HER2 positive metastatic breast cancer.

Outcome:
Recommended

8 Recommended listing

8.1 Restrictions to be finalised.

9 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.

10 Sponsor's Comment

Roche welcomes the PBAC's recommendations and will work with Government to ensure listing of pertuzumab, trastuzumab and trastuzumab emtansine for the treatment of patients with metastatic breast cancer in a timely manner.