

4.2 TRASTUZUMAB, powder for IV infusion, 60 mg and 150 mg, Herceptin®, Roche Products Pty Limited

1 Purpose of Application

- 1.1 Section 100, Authority Required, Restricted Benefit listing for trastuzumab for treatment of HER2 positive, metastatic (equivalent to stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction.

2 Requested listing

- 2.1 Requested PBS listing: Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TRASTUZUMAB Powder for IV infusion, 60 mg			Published prices: \$7,107.48 (public) \$7,183.52 (private)	Roche Herceptin Products Pty Limited
TRASTUZUMAB Powder for IV infusion, 150 mg	1000 mg	0	Effective prices : \$ [REDACTED] (public) \$ [REDACTED] (private)	

Category / Program	Section 100 – Efficient Funding of Chemotherapy Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Metastatic (Stage IV)
Condition:	HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction
PBS indication:	Metastatic (Stage IV) HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction
Treatment phase:	Initial treatment
Restriction level / method:	<input checked="" type="checkbox"/> Authority Required - In Writing

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<p>Clinical criteria:</p>	<p>Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by both (a) immunohistochemistry (IHC)2+ OR IHC3+ AND (b) in situ hybridisation (ISH) results based on both >6 copies of HER2 AND the ratio of HER2:chromosome 17 being >2 either in the primary tumour material or a metastatic lesion.</p> <p>AND</p> <p><u>Patient must commence treatment concurrently with cisplatin and either capecitabine or 5 fluorouracil OR cisplatin and either capecitabine or 5 fluorouracil.</u></p> <p>AND</p> <p><u>Patient must not have received prior trastuzumab and/or prior chemotherapy for metastatic disease.</u></p> <p>AND</p> <p><u>Patient must have a WHO performance status of 2 or less.</u></p> <p>AND</p> <p>The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure.</p>
<p>Prescriber instructions</p>	<p>Authority applications for initial treatment must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed [name TBC] authority application form which includes a copy of the pathology report from an Approved Pathology Authority confirming the presence of HER2 overexpression defined as IHC2+ or IHC3+ and the presence of HER2 gene amplification by in situ hybridisation (ISH) defined as both >6 copies of HER2 and the ratio of HER2: chromosome 17 being >2 and tick a box to state the patient has Stage IV disease.</p> <p>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval and then at 3 monthly intervals during treatment.</p>
<p>Administrative advice</p>	<p>No applications for increased maximum quantities and/or repeats will be authorised.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p>

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Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
TRASTUZUMAB Powder for IV infusion, 60 mg			Published prices: \$5,253.13 (public) \$5,328.95 (private)	Roche Herceptin Products Pty Limited
TRASTUZUMAB Powder for IV infusion, 150 mg	750 mg	0	Effective prices: \$ [REDACTED] (public) \$ [REDACTED] (private)	

Category / Program	Section 100 – Efficient Funding of Chemotherapy Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Metastatic (Stage IV)
Condition:	HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction
PBS indication:	Metastatic (Stage IV) HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction
Treatment phase:	Continuing treatment
Restriction level / method:	<input checked="" type="checkbox"/> Authority Required - Telephone
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must not have progressive disease. AND The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure.
Prescriber instructions	Where a patient has a break in trastuzumab therapy of less than 6 weeks from when the last dose was due, authority approval will be granted for a new loading dose. Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), at 3 monthly intervals during treatment.
Administrative advice	No applications for increased maximum quantities and/or repeats will be authorised. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

The requested restriction differs from the previous submission in that:

- Patients with stage III cancer are excluded from the restriction. This was recommended by the PBAC. The ESC noted that the proposed restriction sought to limit the use of trastuzumab to patients with previously untreated metastatic disease until disease progression.
- HER2 positivity must be demonstrated in tumour material by both (a) IHC2+ or IHC3+ and then (b) ISH results based on both >6 copies of HER2 and the ratio of HER2:chromosome 17 being >2. This was recommended by MSAC. The submission indicated that this should be demonstrated either in the primary tumour or in a metastatic lesion. There are concerns that the two tumour material sources may result in differing HER2 results. Noting that most patients present with Stage IV disease in clinical practice, MSAC foreshadowed a preference for

testing the metastasis rather than the primary tumour although it also indicated that testing the primary tumour should not be excluded. This is a matter to be re-considered by the July 2015 MSAC meeting.

- Authority applications for initial treatment must be made in writing.
- It specifies that where a patient has a break in trastuzumab therapy of less than six weeks from when the last dose was due, authority approval will be granted for a new loading dose. This is consistent with the wording used in the continuing treatment restriction for trastuzumab in early stage and metastatic breast cancer.

- 2.2 The requested basis for listing is cost-utility analysis compared with no HER2 testing followed by cisplatin + 5-fluorouracil (CF) or cisplatin + capecitabine (CX).

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 TGA status: trastuzumab was TGA registered on 3 December 2010 for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.
- 3.2 Trastuzumab was previously considered twice for this indication. The first submission was not recommended in July 2011 citing a high and uncertain ICER, and the second submission was deferred in November 2012 pending further MSAC advice.

Table 1: Summary of the previous submission and current resubmission

	Submission considered in November 2012	Current resubmission
Restriction	HER2 positive advanced (equivalent to stage III or IV) adenocarcinoma of the stomach or gastro-oesophageal junction, in patients who have not received prior treatment for advanced disease, in combination with cisplatin and either capecitabine or 5-fluorouracil, with a WHO performance status of 2 or less. PBAC comment: The PBAC reaffirmed its previous proposal to exclude patients with stage III disease from any recommended restriction.	HER2 positive advanced (<u>equivalent to stage IV</u>) adenocarcinoma of the stomach or gastro-oesophageal junction, in patients who have not received prior treatment for <u>metastatic disease</u> , in combination with cisplatin and either capecitabine or 5-fluorouracil, with a WHO performance status of 2 or less.
HER2 definition	1) ISH+ 2) ToGA ITT population (IHC0/ISH+ or IHC1+/ISH+ or IHC2+/ISH+ or IHC3+) 3) IHC2+/ISH+ or IHC3+ 4) IHC3+ 5) IHC2+/ISH+ or ISH3+/ISH+ (base case) 6) IHC3+/ISH+ PBAC comment: None MSAC comment: The definition of HER2 “positive” in a PBS restriction for trastuzumab in metastatic gastric cancer should be both (a) either IHC2+ or IHC3+ and then (b) ISH results showing >6 copies of HER2 and the ratio of HER2:chromosome 17 being >2 ¹ .	IHC2+ or IHC3+ and then confirmed using ISH based on both >6 copies of HER2 and the ratio of HER2:chromosome 17 being >2 either in the primary tumour or a metastatic lesion.

¹ Ibid., p13 and p15.

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	Submission considered in November 2012	Current resubmission
Effective price of trastuzumab	60 mg vial: \$ [REDACTED] 150 mg vial: \$ [REDACTED] ([REDACTED] % discount) PBAC comment: None	60 mg vial: \$ [REDACTED] 150 mg vial: \$ [REDACTED] ([REDACTED] % discount) The application of a [REDACTED] % discount results in an ex-manufacturer price of \$ [REDACTED] for a 60 mg vial and \$ [REDACTED] for a 150 mg vial. The Pre-Sub-Committee Response stated 'The correct effective prices for the DMPQ of 750mg are \$ [REDACTED] (public) and \$ [REDACTED] (private) and for the DMPQ of 1000mg are \$ [REDACTED] (public) and \$ [REDACTED] (private).
Comparator	Cisplatin plus a fluoropyrimidine (either 5-FU or capecitabine) (CF or CX). Argues that Yun et al (2010) found that ECX and CX are not significantly different in terms of PFS, and by extension ECF and CF are not different. Used CF and ECF in economic model. PBAC comment: None	Cisplatin plus a fluoropyrimidine (either 5-FU or capecitabine) (CF or CX). Used CF in economic model.
Evidence	ToGA trial, ITT analysis and subgroup analysis (see HER2 definition scenarios). PBAC comment: None. MSAC comment: The estimate of trastuzumab incremental effectiveness in the economic evaluation presented to PBAC should reflect the intention-to-treat (ITT) results of the ToGA trial ²	ToGA trial with longer follow-up (i.e. to 7 January 2010 rather than to 7 January 2009), ITT analysis and subgroup analysis (see HER2 definition scenario).
Economic model	Simplified cost-utility model incorporating only HER2+ patients and comparing treatment with HCF versus CF (15.8%) or ECF (84.2%). PBAC comment: No convincing information had been provided to address its previous concerns over the use of triplet chemotherapy costs in the modelling whilst projecting doublet chemotherapy outcomes from the ToGA trial. The ESC noted the resubmission adjusted the economic model in response to the PBAC concerns from previous evaluation as detailed in Table A.1 of the resubmission (including average patient weight based on ToGA not Australian data, cost of hospitalisation for associated diarrhoea, reservations with utilities used).	Cost-utility model incorporating all Stage III and IV patients. Compares testing for HER2 status with HER2+ patients treated with HCF and HER2- patients treated with CF, versus no test/no drug (everybody treated with CF). The ESC noted the revised economic analysis addressed these concerns. The residual issue about the model for the PBAC is the omission of an ICER/QALY based on the longer-term follow-up of ToGA for standard ITT population.
Testing accuracy	26.2% HER2+ (scenario 5), 100% accuracy (ToGA trial and GaTHER study). PBAC comment: Underestimated the... likely extent of false test results under less optimal circumstances than for the ToGA trial... MSAC comment: the sensitivity analyses of the economic evaluation presented to PBAC should appropriately examine the likely extent of proportions of false-positive test results and false-negative test results in Australia compared with those of the evidentiary standard ³	[REDACTED] % HER2+ True positive: [REDACTED] % True negative: [REDACTED] %

² Ibid., p14 and p16.

³ Ibid., p16.

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	Submission considered in November 2012	Current resubmission
Clinical evidence in economic model	HCF and ECF/CF: ToGA trial only, ITT analysis and subgroup analysis (see HER2 definition scenarios). PBAC comment: None	HCF and CF: ToGA trial only, subgroup analysis (see HER2 definition scenarios)
Re-testing	0% of samples are retested. PBAC comment: Underestimated the... the extent of retesting (likely greater than the 10% assumed)... MSAC comment: A re-testing rate of 5% would reasonably reflect the rate of indeterminate results from an initial test ⁴	5% of samples are retested
Extrapolation	Weibull distribution from median follow-up to 5 years. PBAC comment: None	PFS: Log-logistic and Weibull from 12 months to 5 years. Overall survival: Gamma and Weibull from median follow-up to 5 years.
Utilities	PFS state: ■■■ (both treatment groups) Post-progression state: ■■■ PBAC comment: None	PFS state: ■■■ (both treatment groups) Post-progression state: ■■■
Duration of treatment	HCF: Trastuzumab: ■■■ cycles Cisplatin: ■■■ cycles Fluoropyrimidine: ■■■ cycles (ToGA trial) CF: Cisplatin: ■■■ cycles Fluoropyrimidine: ■■■ cycles (ToGA trial) PBAC comment: None	HCF, true positive: Trastuzumab: ■■■ cycles Cisplatin: ■■■ cycles Fluoropyrimidine: ■■■ cycles HCF, false positive: Trastuzumab: ■■■ cycles Cisplatin: ■■■ cycles Fluoropyrimidine: ■■■ cycles (false positive) CF, false negative: Cisplatin: ■■■ cycles Fluoropyrimidine: ■■■ cycles CF, true negative: Cisplatin: ■■■ cycles Fluoropyrimidine: ■■■ cycles
Chemotherapy administration settings	38.54% public hospital outpatients 61.46% private inpatients in private hospitals PBAC comment: None	62.16% public hospital outpatients 37.84% private hospital outpatients
Chemotherapy administration costs	\$■■■ public hospital outpatients \$■■■ private inpatients in private hospitals PBAC comment: None	\$■■■ public hospital outpatients \$■■■ private hospital outpatients
Cardiac function testing	ECG x 3 per course ECHO x 3 per course MBS fees as of April 2012 PBAC comment: Underestimated the... costs of multiple gated acquisition scans associated with trastuzumab.	ECG x 3 per course ECHO x 3 per course MUGA x 1 per course MBS fees as of January 2015
Cost of adverse events	Diarrhoea: 5% of patients receiving HCF, \$■■■ (GP visit + loperamide). PBAC comment: None	Diarrhoea: 3.7% of patients receiving HCF, \$■■■ (hospitalisation)
ICER	\$45,000 - \$75,000/QALY (Scenario 5)	\$45,000 - \$75,000/QALY
Net cost to PBS / MBS over 5 years excluding co-payments	Less than \$20 million/ less than \$10 million (Scenario 5)	Less than \$10 million/ less than \$10 million The resubmission proposed that a subsidisation cap be applied and any expenditure above this cap would

⁴ Ibid., p14 and p16.

	Submission considered in November 2012	Current resubmission
		trigger a ■■■% rebate to the Government.
PBAC decision	Deferred to obtain advice, including from MSAC, on the optimal algorithm for implementing HER2 testing in Australia.	-
MSAC decision	Deferred the application until such time as PBAC makes a decision regarding the corresponding PBS listing of trastuzumab ⁵ .	-

CF/CX=cisplatin/fluoropyrimidine; ECF/ECX=epirubicin/cisplatin/fluoropyrimidine; ECG: electrocardiogram; ECHO: echocardiogram; HCF/HCX=trastuzumab/cisplatin/fluoropyrimidine; IHC=immunohistochemistry; ISH=in situ hybridisation; ITT=intent to treat; MUGA: Multigated Acquisition Scan; PFS: progression-free survival
Source: compiled during the evaluation.

4 Clinical place for the proposed therapy

- 4.1 In 2011 there were 2,093 cases of gastric cancer and 1,126 deaths⁶. The 5-year relative survival rate was 27% in 2006 – 2010⁷.
- 4.2 It was proposed that the HER2 status of all patients with inoperable locally advanced, recurrent and metastatic disease would be tested, and that only HER2+ patients⁸ with metastatic disease would be eligible for treatment with trastuzumab.

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

5 Comparator

- 5.1 No HER2 testing followed by CF or CX. This is unchanged from the previous submission and is appropriate.

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 that no consumer comments were received for this item, but acknowledged the consumer comments provided at the consideration during the November 2012 meeting.

⁵ Ibid., p15.

⁶ AIHW Australian Cancer Incidence and Mortality (ACIM) book

⁷ AIHW (2012) Cancer survival and prevalence in Australia: period estimates from 1982 to 2010, Cat no. CAN 65.

⁸ Defined according to the MSAC definition of HER2 positivity demonstrated by both (a) IHC2+ or IHC3+ and then (b) ISH results based on both >6 copies of HER2 and the ratio of HER2:chromosome 17 being >2.

Clinical trials

- 6.3 The resubmission is based on one head-to-head trial comparing trastuzumab + cisplatin + fluoropyrimidine (5-fluorouracil or capecitabine) (HCF/HCX) with cisplatin plus fluoropyrimidine (5-fluorouracil (CF) or capecitabine (CX)) (n=594): the ToGA trial. This is unchanged from the previous submissions and is reasonable.
- 6.4 Details of the trials presented in the resubmission are provided in the following table.

Table 2: Trials and associated reports presented in the resubmission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial(s)		
ToGA	CBO18255: An open label randomised multicentre Phase III study of trastuzumab in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone as first-line therapy in patients with HER2 positive advanced gastric cancer - Report No. 1032349, Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Sato T, Bang YJ, Gotovkin EA et al. Quality of life in the trastuzumab for gastric cancer trial.	August 2009 The Lancet, 2010; (10) 1-13 Oncologist. 2014; 19(7): 712-19

Source: Table B.2.3, of Section B, drug component of the resubmission

- 6.5 The key features of the direct randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
ToGA trial	594	R, OL 27 mths	Low	Adult patients; performance status of 0-2; inoperable locally advanced and/or metastatic HER2 positive adenocarcinoma of stomach or gastro-oesophageal junction.	OS	Subgroup analysis

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.
Source: Table B.2.4, of Section B, drug component of the resubmission.

- 6.6 The ESC noted that the sponsor argued that the most relevant analyses presented in its resubmission was for the 'High HER2' ToGA subgroup (defined as per the MSAC ISH+ definition). This subgroup captured 361 (60.8%) (HCF:CF 186:175) of the original randomisation sample of 594. Median follow-up duration was marginally longer in the HCF treatment arm (26.7 months vs 25.6 in the CF comparator arm). This represented an additional 8.1 and 8.5 months median follow-up for the HCF and CF arms respectively, when compared to the ITT analysis considered at the November 2012 PBAC meeting.
- 6.7 The ESC noted that the 'High HER2' subgroup was well balanced across treatment arms with regards to gender, race, region, age, height, weight, prior adjuvant chemotherapy, prior anthracycline therapy and ECOG performance status. However the assumption of balance for unmeasured confounders across the originally randomised treatment arms no longer holds in the sub-group analysis and thus residual bias secondary to imbalance of unobserved confounders may apply.

- 6.8 The Pre-Sub-Committee-Response argued that ‘the recommendation to use the ITT population of ToGA as the basis for estimating effect size in the economic evaluation of trastuzumab is overly conservative’ and cited the letter from Royal College of Pathologists of Australia to MSAC that stated ‘There is no reason to assume the standards of the ToGA trial could not be met in Australia or even surpassed given the stricter definition of HER2 positivity proposed in Australia for gastric cancer’. Though noting the issues surrounding the test was a matter for MSAC, the ESC considered that presentation by the sponsor of a more conservative scenario applying the results of the longer follow-up for the standard ITT population alongside the likely best case scenario represented by applying the ‘High HER2’ subgroup results would be crucial for PBAC decision making.

Comparative effectiveness

Table 4: Results of overall survival and PFS in ToGA

Trial ID	HCF/HCX, median months (95%CI)	CF/CX, median months (95%CI)	Absolute difference	HR (95%CI)	NNT/NNH
Overall survival					
ITT population, November 2012 submission	13.8 (12, 16)	11.1 (10, 13)	2.7	0.74 (0.60, 0.91)	NA
ITT, resubmission (longer follow-up) [#]					NA
‘High HER2’ subgroup (longer follow-up) [^]					NA
Resubmission’s pseudo-ITT subgroup ^{&}					NA
Progression-free survival					
ITT population, November 2012 submission	6.7 (6, 8)	5.5 (5, 6)	1.2	0.71 (0.59, 0.85)	NA
ITT, resubmission (longer follow-up) [#]					NA
‘High HER2’ subgroup (longer follow-up) [^]					NA
Resubmission’s pseudo-ITT subgroup ^{&}					NA

[#] IHC3+ or FISH+, ISH+ was defined as HER2 ratio ≥ 2 ;

[^] IHC2+/3+ and FISH+, ISH+ was defined as HER2 ratio ≥ 2 and gene copy number > 6 ;

[&] IHC3+ or FISH+, ISH+ was defined as HER2 ratio ≥ 2 and gene copy number > 6 ;

CF/CX=cisplatin/fluoropyrimidine; CI=confidence interval; HCF/HCX=trastuzumab/cisplatin/fluoropyrimidine; HR = hazard ratio; ITT = intention to treat; NNT = number needed to treat; NNH = number needed to harm.

Source: Table B.6.3, p16 and Table B.6.5, p17, Section B, drug component of the resubmission, Table 16, p23, Section B Appendix of the November 2012 submission; and Table 43-45, p59-61, Section B appendix of the November 2012 submission, Attachment 4, OS data for MSAC ITT.pdf, Attachment 4, PFS data for MSAC ITT.pdf and calculated during the evaluation. Revisions from Table 1 .

Likelihood-ratio test for interaction analysis with treatment effect assessed by HR (‘High HER2’ subgroup versus its complement subgroup from the longer follow-up of the standard ITT population): P=0.0014 for OS and P=0.0022 for PFS.

- 6.9 MSAC reaffirmed its advice to the Minister that a conservative approach to assessing the cost effectiveness of trastuzumab for HER2 positive gastric cancer would be to base the estimate of effect size on the results from the ITT trial population of the pivotal trial (ToGA) and not on the results from subgroup analyses.

Comparative harms

6.10 Based on the ToGA trial:

- There was no statistically significant difference in the proportion of patients experiencing adverse events between the HCF/HCX and CF/CX arms (ITT population);
- Patients in the HCF/HCX arm experienced about 22% more adverse events than patients in the CF/CX arm (ITT population);
- Under the MSAC definition of ISH positivity, the incidence of treatment-related adverse events was marginally statistically significantly higher in the HCF/HCX arm, compared with the CF/CX arm (█████% vs █████%; RR █████, 95% CI █████, █████, reference=CF,
- The ESC noted there was no difference in the incidence of serious adverse events or cardiac events;
- The incidence of cardiac disorders was slightly higher in the High HER2 HCF arm relative to the CF comparator, although this difference was not statistically significant. The ESC noted the inclusion of cardiac monitoring in the revision of proposed restriction;
- No new or unexpected safety signals were detected in the safety analysis population compared to the known profile of trastuzumab in breast cancer.

Benefits/harms

6.11 A summary of the comparative benefits and harms for HCF/HCX versus CF/CX is presented in the table below.

Table 5: Summary of comparative benefits and harms for HCF/HCX and CF/CX

Benefits						
	HCF/HCX	CF/CX	Absolute difference	HR (95% CI)		
Overall survival, ITT [#] , median months (95%CI) resubmission, longer follow-up						
Overall survival, 'High HER2' subgroup [^] , median months (95%CI)						
Overall survival, resubmission's pseudo-ITT subgroup ^{&}						
PFS, ITT [#] , median months (95%CI) resubmission, longer follow-up)						
PFS, 'High HER2' subgroup [^] , median months (95%CI)						
PFS, resubmission's pseudo-ITT subgroup ^{&}						
Harms						
	HCF/HCX	CF/CX	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				HCF/HCX	CF/CX	
Any grade adverse events, events			1.218 (NR)	956.5	795.9	160.6 (NR)

* 18.6 months and 17.1 months median duration of follow-up with HCF/HCX and CF/CX, respectively.

[#] IHC3+ or FISH+, ISH+ was defined as HER2 ratio ≥ 2 ;

[^] IHC2+/3+ and FISH+, ISH+ was defined as HER2 ratio ≥ 2 and gene copy number > 6 ;

[&] IHC3+ or FISH+, ISH+ was defined as HER2 ratio ≥ 2 and gene copy number > 6 ;

CF/CX=cisplatin/fluoropyrimidine; CI=confidence interval; HCF/HCX=trastuzumab/cisplatin/fluoropyrimidine; HR = hazard ratio; ITT = intention to treat; PFS = progression-free survival; RD = risk difference; RR = risk ratio.

Source: Table B.6.3, p16 and Table B.6.5, p17, Section B, drug component of the resubmission, Table 16, p23, Section B Appendix of the November 2012 submission; and Table 43-45, p59-61, Section B appendix of the November 2012 submission, Attachment 4, OS data for MSAC ITT.pdf, Attachment 4, PFS data for MSAC ITT.pdf, Table B.6.6, p20 of Section B, drug component of the resubmission and Table 53, p72, Section B – Appendix, of the November 2012 submission, Selected_AEs_HighHER2.xls, Sheet 2-SELAE_SAF and p142 of Clinical Study Report_ToGA.pdf and calculated during the evaluation

- 6.12 On the basis of direct evidence presented by the resubmission, the comparison of HCF/HCX and CF/CX in the 'High HER2' subgroup resulted in:
- Approximately months difference in median PFS
 - Approximately months difference in median overall survival.
- 6.13 On the basis of direct evidence presented by the resubmission, the comparison of HCF/HCX and CF/CX in the ITT population resulted in:
- Approximately 1.4 months difference in median PFS
 - Approximately 1.2 months difference in median overall survival.
- 6.14 On the basis of direct evidence presented by the resubmission, the comparison of HCF/HCX and CF/CX resulted in:
- Approximately 160.6 additional adverse events would occur per 100 patients treated over a median duration of follow-up of 18.6 months and 17.1 months with HCF/HCX and CF/CX, respectively.

Clinical claim

- 6.15 The resubmission described trastuzumab in combination with cisplatin plus a fluoropyrimidine (HCF/HCX) as superior in terms of comparative effectiveness and no worse in terms of comparative safety over cisplatin plus a fluoropyrimidine (CF/CX). This is unchanged compared to that presented in the previous submissions.
- The claim of improved effectiveness was previously accepted by the PBAC in July 2011⁹.
 - In November 2012, the PBAC noted that the magnitude of the clinical benefit was small: a statistically significant but clinically borderline increase in the primary outcome of overall survival in the ITT analysis of the ToGA trial (a gain of 2.7 months from a median of 11.1 months without trastuzumab to a median of 13.8 months with trastuzumab). The progression-free survival increased by 1.2 months from a median of 5.5 months without trastuzumab to a median 6.7 months with trastuzumab¹⁰. The ESC noted that the resubmission argued that, in the ‘High HER2’ subgroup (by aligning with the MSAC definition of HER2 positivity) HCF/HCX extended the gain in median overall survival to ■■■ months, and is thus the relevant subgroup to determine the incremental effectiveness of trastuzumab and its clinical significance. HCF/HCX also extended the gain in median PFS to ■■■ months. Whilst the high HER2 subgroup remains balanced with regards to key baseline prognostic factors and confounders, the ESC considered that the subgroup is comparatively underpowered relative to any of the ITT analyses presented.
 - The magnitude of the benefit is uncertain as it was based on an exploratory subgroup analysis. Furthermore, for the ‘High HER2’ subgroup, the gain in PFS (■■■ months) is smaller than the gain in post-progression survival (approximately ■■■ months).
 - A large proportion of patients in the CF arm ended active chemotherapy after six cycles, which may be biased in favour of trastuzumab. However the duration of treatment with CF and CX ultimately depends on the extent to which patients experience toxicity.
 - The claim of no worse safety was not considered reasonable by the PBAC in July 2011¹¹. While there was no statistically significant difference in the proportion of patients experiencing adverse events, patients in the HCF arm experienced about 22% more adverse events than patients in the CF arm from the ToGA trial safety population.
 - In July 2011, the PBAC also noted that the ToGA trial population was a low-risk population for toxicity, obtained by stringent exclusion criteria. A higher trastuzumab-related toxicity profile, compared to the ToGA trial, would be anticipated in clinical practice¹². The resubmission argued that the inclusion of the cardiac monitoring precaution in the proposed PBS restriction should address these concerns.
 - The previous commentary also noted that, if triplet therapy (ECF/ECX) is to replace HCF/HCX, then using the comparison of adverse events in ToGA as a proxy for the comparison of HCF and ECF is likely to bias against trastuzumab,

⁹ [PBAC Public Summary Document \(PSD\), November 2012](#), item 6.9.23

¹⁰ [PBAC Meeting PSD, November 2012](#), p50

¹¹ [PBAC Meeting PSD, November 2012](#), item 6.9.25

¹² [PBAC Meeting PSD, November 2012](#), item 6.9.25

because triplet therapy is likely to have a more severe safety profile than doublet therapy (MSAC 6.2./PBAC 7.7.COM.85).

Economic analysis

- 6.16 Cost-utility analysis. The resubmission presented a revised economic model that takes into account test accuracy, and the expected costs and benefits of treating false-positive patients with trastuzumab and not treating false-negative patients. This was changed from the previous submission. The change meant that sensitivity analyses around the sensitivity and specificity of the tests were able to be conducted.
- 6.17 Whilst the cost-utility analysis uses the ‘High-HER2’ ToGA subgroup effect sizes, the November 2012 MSAC meeting previously advised a preference to use the ToGA ITT for the CUA, a position recently re-affirmed in April 2015. As noted above, the ESC considered presentation by the sponsor of the results of the cost-utility analysis applying the results of the longer follow-up for the standard ITT population would be crucial for PBAC decision making.

Table 6: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case versus 1,306 days in trial*
Outcomes	Life-years gained (LYG) and QALYs
Methods used to generate results	Area Under the Curve (AUC) analysis using Kaplan Meier time-to-event data from the ToGA trial.
Transition probabilities	<p>Patients in the ‘test/drug available’ arm:</p> <ol style="list-style-type: none"> 1. True-positive HER2 result appropriately treated with HCF: Based on the HCF/HCX arm of the ToGA trial with high HER2 expression[^]; 2. False-positive HER2 result inappropriately treated with HCF: Based on the ITT population of the CF/CX arm of the ToGA trial; 3. True-negative HER2 test result appropriately treated with CF: Based on the ITT population of the CF/CX arm of the ToGA trial; 4. False-negative HER2 test result inappropriately treated with CF: Based on patients in the CF/CX arm of the ToGA trial with ‘High HER2’ expression[^]. <p>Patients in the ‘Test/drug not available’ arm treated with CF (HER2 status not assessed): Based on the ITT population of the CF/CX arm of the ToGA trial.</p>

*Maximum follow-up in CF arm of ToGA trial, ‘High HER2’ subgroup

[^] High HER2 expression defined as: IHC2+/ISH+ or IHC3+/ISH+; ISH+ was defined as HER2 ratio ≥ 2 and gene copy number > 6)

Table 7: Key drivers of the model

Description	Method/Value	Impact
Efficacy of HCF/HCX in true-positive and false-negative patients	Based on the 'High HER2' subgroup of ToGA rather than the ITT population	Likely to be high, favours trastuzumab
Efficacy of CF/CX in false-positive and true-negative patients, and the comparator (test/drug not available)	Based on the ITT population of the CF/CX arm of the ToGA trial (there would be more HER2+ patients compared to the corresponding populations supposed to be modelled in these arms)	High, favours trastuzumab
Parametric function used to extrapolate overall survival of patients in 'High HER2' subgroup of the ToGA trial	Gamma function, rather than Weibull function	Moderate, favours trastuzumab
Kaplan-Meier data and parametric function used to extrapolate PFS and overall survival of patients in the ITT population of the ToGA trial	Fitted using data up to 7 January 2009, rather than longer-term follow-up data up to 7 January 2010	Unknown

CF/CX=cisplatin/fluoropyrimidine; ECF/ECX=epirubicin/cisplatin/fluoropyrimidine; HCF/HCX=trastuzumab/cisplatin/fluoropyrimidine; ITT=intention to treat; PFS: progression-free survival
 Source: compiled during the evaluation

Table 8: Results of the stepped economic evaluation

Step and component	Test + trastuzumab available	No test + trastuzumab not available	Increment
Step 1: Trial-based cost per LY gained (truncated at 1306 days)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
LYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra LY gained			\$ [redacted]
Step 2: Modelled cost per LYG (truncated at 5 years)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
LYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra LY gained			\$ [redacted]
Step 3: Modelled cost per QALY gained (truncated at 5 years)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained			\$ [redacted]
Step 3: Modelled cost per QALY gained (truncated at 5 years) – November 2012 submission			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost/extra QALY gained – November 2012 submission			\$ [redacted]

Source: Table D.5.5, p37, Section D of the resubmission and Table D.5.1 p46-Table D.5.7 p49 of section D of the November 2012 submission

- 6.18 The submission presented a base case ICER of \$45,000 - \$75,000/QALY. In this resubmission, the base case economic model has been appropriately re-structured to take into account test accuracy; it is now a test-treat approach. The model previously underestimated the extent of false test results. The health outcomes for true-positives and false-negatives in the model were based on the 'High HER2' subgroup in the HCF arm and CF/CX arm of the ToGA trial, respectively, which is consistent with the resubmission's reliance on this subgroup analysis. The health outcomes for false-positive and true-negative patients, and the comparator (test/drug not available), were based on the ITT population of the CF/CX arm of the ToGA trial. All patients recruited into ToGA had some form of HER2 positivity, as such there are more HER2+ patients in these arms than in a genuinely unselected population. This is acknowledged in the resubmission, and the approach taken is consistent with

previous ESC advice. Although the prognostic value of HER2 status and thus on untreated PFS and untreated OS, is unknown, it was not possible to conduct any sensitivity analysis to assess the consequence of this issue on the results of the model.

- 6.19 The results of the univariate sensitivity analyses presented by the resubmission and additional analyses conducted during the evaluation are shown below. The ESC noted that the ICER was relatively robust to the parameters varied in the sensitivity analysis.

Table 9: Sensitivity analysis results (discounted)

Stepped economic evaluation	Incremental costs	Incremental effectiveness (QALYs gained)	Incremental cost-effectiveness
Base-case (Step 3)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Prevalence of 'High HER2' positivity as per the ToGA study	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Sensitivity and specificity rates are as per ToGA study †	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Sensitivity and specificity rates are as CISH in GaTHER †	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Sensitivity and specificity rates are as SISH in GaTHER †	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
A log logistic function is used to extrapolate overall survival	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
A Weibull function is used to extrapolate overall survival	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
CF treatment ceases at cycle six	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Inclusion of costs of subsequent chemotherapy after disease progression*	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Reclassification of private hospital scripts	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utility for HCF patients free from progression is based on 25 weeks of data from ToGA (0.7910)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utility for progressed disease is 0.5	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utility for progressed disease is 0.6	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Using utility values from Shiroiwa 2011	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Cost of IV administration costs	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Cost of AEs includes GP costs and loperamide for grade 3 diarrhoea	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Cost of palliative care = \$6,073	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Cost of cisplatin	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

* In the ToGA trial, 38.4% and 2.7% of patients in the HCF/CX arm received subsequent chemotherapy and surgery after disease progression, respectively, and 42.8% and 4.5% of patients in the CF/CX arm received subsequent chemotherapy and surgery after disease progression, respectively. It was assumed that patients receiving subsequent chemotherapy receive three months of treatment with carboplatin and cyclophosphamide. For patients receiving subsequent surgery, the unit cost was based on the AR-DRG cost for digestive malignancy with catastrophic or severe complications (AR-DRG Item G60B). Overall the discounted cost applied to patients who received HCF was \$ [REDACTED] and to patients who received CF was \$ [REDACTED].

- 6.20 Whilst assuming underlying gamma and log-logistic distribution functions appeared to be reasonable for capturing the overall fit of the high HER2 OS and PFS estimates respectively (as measured by the function with the smallest Akaike Information Criterion), the ESC noted the effect of fitting parametric functions to the longer-term follow-up data of the ITT population of the CF/CX arm of the ToGA trial was not assessed in any sensitivity analyses in the resubmission. The PSCR presented

updated Weibull distributions of OS and PFS used to extrapolate beyond the trial data, these were based on the recent data cut (to 7 January 2010) which was also the source of the Kaplan-Meier estimates used in the resubmission. The ESC noted that the updated distributions provided a good fit to the tail of the Kaplan-Meier curves and, when applied to the ITT population of the CF/CX arm, the ICER/QALY increased from \$45,000 - \$75,000 to \$45,000 - \$75,000.

- 6.21 The pre-PBAC response claimed that if an additional 5% reduction was applied to the ex-manufacturer price of trastuzumab through the amendments to the *National Health Act 1953* following implementation of the PBS Access and Sustainability Package (June 2015), the ICER/QALY would be \$45,000 - \$75,000.
- 6.22 The resubmission also conducted a sensitivity analysis using the longer-term follow up data for another post hoc subgroup of the ITT population that included patients if they were IHC3+ or ISH+ as defined using the ISH component of the MSAC definition of HER2 positivity (i.e. a pseudo-ITT subgroup). Although labelled by the resubmission as an ITT analysis, these results were not of the full ITT trial population of the pivotal trial (ToGA), which was recommended by MSAC (MSAC Meeting Minutes, 1-2 April 2015). The estimated ICER of the resubmission's sensitivity analysis was \$45,000 - \$75,000/QALY gained. A comparison of the numerical results of the standard ITT population and the "pseudo-ITT" population from the ToGA trial indicated that the ICER from this pseudo-ITT subgroup was underestimated in this sensitivity analysis compared to a sensitivity analysis based on the standard ITT population.
- 6.23 The pre-PBAC response provided an economic analysis based on the longer-term follow-up of ToGA for standard ITT population. This ITT model used the following:
- longer-term follow-up KM time-to-event data for the ITT population;
 - extrapolation of time-to-event data performed (from the updated median duration of follow-up) using the updated Weibull function (presented in the PSCR);
 - incorporating longer-term extent of exposure data from the ITT population;
 - utility scores (elicited using Viney 2014) from the ITT population.
- 6.24 The PBC noted that the resulting ICER was \$105,000 - \$200,000/QALY, and that this model could not be fully evaluated as it was provided late in the lead up to the PBAC meeting.

Drug cost/patient/course: \$ [REDACTED]

- 6.25 It was estimated that patients receive [REDACTED] (3 weekly) cycles of treatment ([REDACTED] days). There is a potential for trastuzumab to be used post disease progression, however this issue would be addressed by proposing a subsidisation cap.

Estimated PBS usage & financial implications

- 6.26 This resubmission was not considered by DUSC. The resubmission used an epidemiology approach to estimate the financial implications of listing trastuzumab.

Table 10: Estimated use and financial implications

	2016	2017	2018	2019	2020
Estimated extent of use					
Number treated	█	█	█	█	█
Number treated - Nov 2012 (scenario 5)	█	█	█	█	█
Uptake rate			%		
Uptake rate Nov 2013			%		
Vials	█	█	█	█	█
Vials - Nov 2012 (scenario 5)	█	█	█	█	█
Estimated net cost to PBS/MBS					
Net cost to PBS	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS - Nov 2012 (scenario 5)	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS - Nov 2012 (scenario 5)	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated total net cost					
Net cost PBS/MBS	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost PBS/MBS Nov 2012	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Compiled during the evaluation

- 6.27 The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS/MBS would be less than \$10 million. The potential for the net cost/year to the PBS to be greater (e.g. due to treatment accuracy or treatment past progression) is constrained by the proposed subsidisation cap (see below).

Financial Management – Risk Sharing Arrangements

- 6.28 The resubmission proposed that a subsidisation cap be applied based on a mean duration of exposure for all patients treated with trastuzumab in the ToGA trial (█ cycles). Any PBS expenditure above this cap would trigger a █% rebate to the Government. The aim of this cap would be to address expenditure concerns of Government surrounding use beyond progression.

Table 11: Proposed subsidisation caps for expenditure on trastuzumab

	2016	2017	2018	2019	2020
Subsidisation cap*	\$ █	\$ █	\$ █	\$ █	\$ █

* Based on drug acquisition cost (effective price including █% reduction on the ex-manufacturer price) of trastuzumab less patient co-payments

- 6.29 The pre-PBAC response noted that the caps fully mitigate the financial risk to PBS expenditure from use in patients where the cost-effectiveness has not been assessed or agreed, including:
- patients with earlier stages of gastric cancer;
 - patients with metastatic disease that has progressed whilst on treatment with trastuzumab;
 - patients whose disease does not truly meet the stringent MSAC definition of HER2 positivity.
- 6.30 The PBAC recommended a risk share arrangement (RSA) to minimise the risk of usage beyond progression of disease and usage by patients with false-positive test

results. The PBAC considered that the RSA should be negotiated in a manner that could be implemented by the Department, based on the subsidisation cap proposed in Section F of the resubmission. The PBAC advised that MSAC could consider whether the █████% rebate in the RSA, if triggered, should be extended to include some proportion (up to █████%) of MBS (testing cost) expenditure.

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

7 PBAC Outcome

- 7.1 The PBAC recommended extending the listing of trastuzumab under Section 100 (Efficient Funding of Chemotherapy Drugs Program) for the treatment of HER2 positive, metastatic (equivalent to stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction. This recommendation reflected a wide range of high to very high incremental cost-effectiveness ratios that were acceptable in the context of a modest but potentially meaningful extension of overall survival in a difficult to treat cancer affecting a small number of patients, and with effective controls to limit the financial costs to the PBS.
- 7.2 The PBAC noted the supportive advice from the November 2012 and April 2015 MSAC meetings relating to HER2 testing in the context of this disease.
- 7.3 The PBAC noted the proposed restriction had been modified following the November 2012 PBAC and MSAC meetings and considered that:
- The proposed population of patients with HER2 positive advanced (equivalent to stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior treatment for metastatic disease was appropriate.
 - The final criterion for defining HER2 positivity should align with the outcome of the consideration of HER2 testing by MSAC at its July 2015 meeting. The PBAC noted MSAC foreshadowed a preference for testing the metastasis rather than the primary tumour although it also indicated that testing the primary tumour should not be excluded.
- 7.4 The PBAC recalled that it had accepted that no HER2 testing followed by CF or CX was the appropriate comparator.
- 7.5 The PBAC noted the 'High HER2' subgroup analysis of the ToGA trial was presented as the basis for estimating the comparative effectiveness of trastuzumab in Australia. The resubmission reported the progression-free survival (PFS) and overall survival (OS) in the 'High HER2' subgroup of the ToGA trial generated for the resubmission to align with the MSAC-recommended definition of HER2 positivity. The subgroup analysis, on approximately 61% of the randomised ToGA study population, estimated the relative health gain in this population to be considerably greater than either the original intent-to-treat (ITT) population or the resubmitted ITT population with 12 months additional follow-up or post-hoc pseudo-ITT (included patients if IHC3+ or ISH+ as defined using the ISH component of the MSAC definition) population. The PBAC considered that patients identified to be 'High HER2' would benefit from treatment, but the magnitude of the benefit in the 'High HER2' population proposed for PBS listing was uncertain as the estimate provided was based on an exploratory subgroup analysis and was comparatively under-powered relative to any of the ITT-

based effect sizes presented. The PBAC noted the paradoxical outcomes for the 'High HER2' subgroup, where the gain in PFS (■ months) was smaller than the gain in post-progression survival (approximately ■ months), yet in the ITT and pseudo-ITT population, the gain in PFS (1.2 and 1.8 months, respectively) was greater than the gain in post-progression survival (0.2 and 1.3 months, respectively). This latter finding was considered to be more plausible and as consequence the PBAC considered the estimated median survival gain of ■ months was likely to be an overestimate of the incremental benefit of the trastuzumab combination. The PBAC noted that the pre-ESC response argued that OS rather than PFS was the preferred measure of treatment benefit and that PFS was not a valid surrogate. These comments were contrary to previously stated views regarding cancer drugs which indicated that PFS rather than OS was the most patient relevant outcome and that PFS was a valid surrogate for survival.

- 7.6 The PBAC recalled that, in July 2011, it had noted that no incremental effect was detected on quality of life, but patients in the trastuzumab arm of the trial experienced 22% more adverse events than patients in the control arm of the trial.
- 7.7 The PBAC noted that the resubmission appropriately presented a revised economic model that took into account test accuracy, and the expected costs and benefits of treating false-positive patients with trastuzumab and not treating false-negative patients. The PBAC noted that the resubmission acknowledged that the scenario of test/drug not available were based on the ITT population of the CF/CX arm of the ToGA trial and all patients recruited into ToGA had some form of HER2 positivity, as such there are more HER2+ patients in these arms than in a genuinely unselected population.
- 7.8 The PBAC noted that when resubmission presented the best case scenario of the High HER2 population, the ICER, updated in the PSCR, was \$45,000 - \$75,000/QALY.
- 7.9 At its April 2015 meeting, MSAC reaffirmed its advice to the Minister that a conservative approach to assessing the cost effectiveness of trastuzumab for HER2 positive gastric cancer would be to base the estimate of effect size on the results from the ITT trial population of the pivotal trial (ToGA). The PBAC agreed with MSAC that this approach would provide the most likely worst case scenario, and thus would allow the Committees to consider the range of cost-effectiveness with the listing of this treatment. The pre-PBAC estimated that cost-effectiveness based on the results from the ITT trial population was \$105,000 - \$200,000/QALY. The PBAC concluded that the incremental cost-effectiveness of trastuzumab for the new gastric cancer indications lay within the range of \$45,000 - \$75,000/QALY to \$105,000 - \$200,000/QALY, and reflected the wide range of effectiveness estimates generated from ToGA and its subgroup analyses.
- 7.10 Given the uncertain magnitude of clinical benefit and the high to very high ICERs despite the reduced effective prices of trastuzumab being offered compared to previous submissions, the limited treatment options available for this patient group, the overall small financial implications to the PBS, and the proposed subsidisation cap by the sponsor were important considerations for the PBAC in deciding to recommend trastuzumab as requested.

- 7.11 The PBAC noted that, given the MSAC definition of HER2 positivity compared with that adopted for recruitment in the ToGA trial, the submission estimated that less than 10,000 patients would be treated per year, and that the cost to Government would be less than \$10 million per year. The PBAC considered that the subsidisation cap proposed by the sponsor would mitigate against the financial risk to the Commonwealth of a greater use of trastuzumab than estimated in the submission.
- 7.12 The PBAC noted that a form of trastuzumab which could be delivered by the subcutaneous route was being considered at the same meeting (refers to item 5.18) and the current product information for this form did not include treatment of HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction.
- 7.13 The PBAC recommended, under Section 101(3BA) of the *National Health Act 1953*, that trastuzumab should not be treated as interchangeable on an individual patient basis with another drug.
- 7.14 The PBAC advised that trastuzumab is not suitable for prescribing by nurse practitioner, as Section 100 medicines are out-of-scope for prescribing by nurse practitioners.
- 7.15 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:

Recommended

8 Recommended listing

Amend existing listing as follows:

To be finalised following MSAC consideration of the HER2 testing.

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 recommendation and will work with Government to ensure listing of trastuzumab for the treatment of patients with metastatic gastric cancer in a timely manner.