

5.18 TRASTUZUMAB, 600 mg/5 mL solution for subcutaneous injection, Herceptin® SC, Roche

1 Purpose of Application

- 1.1 The minor submission sought the Pharmaceutical Benefits Scheme (PBS) listing of a new, subcutaneously (SC) administered, formulation of trastuzumab for patients with human epidermal growth factor receptor 2 (HER2) positive breast cancer.

2 Requested listing

- 2.1 The submission sought the same restriction for trastuzumab SC as currently exists for trastuzumab intravenous (IV) injection in early breast cancer, locally advanced breast cancer, and metastatic breast cancer.
- 2.2 Consistent with the proposed listing arrangements for rituximab SC (recommended at November 2014 PBAC meeting), the submission proposed that trastuzumab SC be made available under General Schedule (see proposed restriction below) and Schedule 2 of the section 100 'Related Pharmaceutical Benefits' to the National Health (Efficient Funding of Chemotherapy) Special Arrangement 2011.
- 2.3 The submission based the proposed restriction for three weekly SC trastuzumab on the current restriction for three-weekly administration of intravenous trastuzumab in early and metastatic breast cancer.

Treatment for HER2-positive early breast cancer and locally advanced breast cancer (abridged restriction)

Name, Restriction, Manner of administration and form	Max. Qty	Nº. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TRASTUZUMAB Solution for subcutaneous injection 600 mg/5 mL	600 mg	3	\$ [REDACTED] (public) \$ [REDACTED] (private)	Herceptin® Roche

Category / Program:	GENERAL – General Schedule (Code GE)
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
Episodicity:	Previously untreated
Condition:	HER2-positive early breast cancer Locally advanced HER2-positive breast cancer
PBS Indication:	Patient with HER2-positive early or locally advanced breast cancer
Treatment phase:	Initial treatment and continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic OR <input type="checkbox"/> Streamlined

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Treatment criteria:	Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy. HER2-positivity must be demonstrated by in situ hybridisation (ISH).
Clinical criteria:	<p><u>Locally advanced breast cancer:</u> Patient must commence treatment concurrently with neoadjuvant chemotherapy 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,</p> <p><u>Early breast cancer:</u> Patient must commence treatment concurrently with adjuvant chemotherapy AND Patient must have undergone surgery, 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</p> <p><u>For continuing patients:</u> Patient must have previously been issued with an authority prescription for this drug for this condition</p>
Population criteria:	Patients with HER2-positive early breast cancer, or locally advanced breast cancer
Prescriber Instructions:	<p><u>For initial treatment:</u> Authority applications for initial treatment must include: (a) a completed authority prescription form; and (b) a completed Early Breast Cancer - PBS Supporting Information Form which includes: (i) a copy of the pathology report from an Approved Pathology Authority confirming the presence of HER2 gene amplification by in situ hybridisation (ISH); and (ii) a copy of the signed patient acknowledgement form.</p> <p>Cardiac function must be tested by a suitable method including, for example, ECHO or MUGA, prior to seeking the initial authority approval and then at 3 monthly intervals during treatment.</p>

Treatment for HER2-positive metastatic breast cancer (abridged restriction)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TRASTUZUMAB Solution for subcutaneous injection 600 mg/5 mL	600	3	\$ [REDACTED] (Public) \$ [REDACTED] (Private)	Herceptin® Roche

Category / Program:	GENERAL – General Schedule (Code GE)
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
Episodicity:	Previously untreated
Condition:	HER2-positive metastatic breast cancer
PBS Indication:	Metastatic (Stage IV) HER2-positive breast cancer

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required – Electronic OR <input type="checkbox"/> Streamlined
Treatment criteria:	Treatment should continue until progression of disease
Clinical criteria:	Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) either in the primary tumour or a metastatic lesion, AND The treatment must not be in combination with nab-paclitaxel, 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.
Population criteria:	Patients with HER2-positive metastatic breast cancer
Prescriber Instructions:	<u>For initial treatment:</u> Authority applications for initial treatment must include: (a) a completed authority prescription form; and (b) a completed Late stage metastatic breast cancer Initial PBS authority application form which includes a copy of the pathology report from an Approved Pathology Authority confirming evidence of HER2 gene amplification in the primary tumour or a metastatic lesion by in situ hybridisation (ISH) and tick a box to state the patient has Stage IV disease. 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 <u>For continuing treatment:</u> Where a patient has a break in trastuzumab therapy of more than 1 week 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).

2.4 The PBAC noted that the final restriction for trastuzumab IV in metastatic breast cancer contains a grandfather clause:

- Patient must have previously received non-PBS-subsidised treatment with this drug for this condition before 1 July 2015, 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.

2.5 The Pre-PBAC Response stated that replication of this grandfather clause for trastuzumab SC would be advantageous as it would allow patients who are 'long-term responders' access to the SC formulation. It further noted that as many of these 'long term responders' may have been diagnosed as IHC3+, prior to the widespread use of in situ hybridization (ISH) testing they would not be eligible for PBS funded SC trastuzumab via the proposed initial restriction. The PBAC considered it was appropriate that this grandfather clause should be extended to trastuzumab SC.

- 2.6 To mirror the trastuzumab IV restriction, the PBAC considered that it was appropriate that the initial script for trastuzumab SC be a written authority with no repeats and continuing scripts be a telephone authority with three repeats.

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

3 Background

- 3.1 TGA status at time of PBAC consideration: trastuzumab SC was approved with the Therapeutic Goods Administration (TGA) on 17 March 2015 for:
- the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy
 - the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab
 - 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 At the time of consideration, trastuzumab IV formulation was PBS listed for:
- Locally advanced HER2-positive breast cancer, commencing concurrently with neoadjuvant chemotherapy; and
 - Early HER2-positive breast cancer, commencing concurrently with adjuvant chemotherapy.
 - Metastatic (Stage IV) HER2 positive breast cancer.
- 3.3 Trastuzumab SC had not been previously considered by the PBAC.

4 Clinical place for the proposed therapy

- 4.1 Trastuzumab is a monoclonal antibody that is directed against the extracellular domain of the HER2 protein. Trastuzumab SC formulation contains a fixed dose of 600 mg and recombinant human hyaluronidase PH-20 (rHuPH-20) as an excipient. rHuPH-20 is an enzyme that temporarily degrades interstitial hyaluronan in the subcutaneous space, thereby increasing the volume of drug that can be administered subcutaneously and aiding delivery of trastuzumab to the circulation.
- 4.2 The submission stated that trastuzumab SC offers a convenient alternative to the IV formulation because it can be administered over two to five minutes. Other potential benefits of the SC formulation included providing an alternative route of administration for patients with poor venous access.
- 4.3 The submission provided survey data from the PrefHer study, an international, randomised, two-cohort crossover study comparing early breast cancer patient

preference for trastuzumab SC and trastuzumab IV, to support the claim that the SC formulation was a more convenient alternative to IV administration. Patients (n=248) were randomised to receive 4 cycles of 600 mg adjuvant trastuzumab SC (administered via Single-Injection Device [SID, cohort 1] or hand-held syringe [from vial, cohort 2]) followed by 4 cycles of trastuzumab IV, or the reverse sequence. After the crossover period, patients continued intravenous or subcutaneous trastuzumab to complete a total of 18 treatment cycles. This showed that the majority of patients (86.1%) preferred trastuzumab SC to IV because it either saved time or resulted in less pain and discomfort.

- 4.4 The submission also discussed the results from the time and motion sub-studies of the PrefHer study to support its claim that trastuzumab SC was time and resource saving. It showed that mean patient time (including both chair and non-chair time) was considerably shorter for patients receiving trastuzumab SC versus trastuzumab IV.

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

5 Comparator

- 5.1 The submission nominated trastuzumab powder for IV infusion as the main 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 one organisation via the Consumer Comments facility on the PBS website. The comment described a range of benefits of treatment with trastuzumab SC including greater convenience for patients and clinics in terms of time spent at treatment sites and the ability for patients to be treated in their own homes, reducing the need for travel and time away from family and work. The organisation noted that this was particularly important for patients living in rural and remote areas.
- 6.3 It was also noted that trastuzumab SC may result in increased out of pocket expenses for patients in the private health system, as the appointment with the oncology nurse to administer it will not be covered by private health insurance. The comment states that full financial disclosure should be provided to patients before commencing treatment.

Clinical trials

6.4 The minor submission presented the results of one pivotal trial, HannaH, a phase III, randomised, open-label trial (see Table 1). The HannaH trial compared trastuzumab SC 600 mg/5 mL to trastuzumab IV (8 mg/kg loading dose and 6 mg/kg continuing dose) in patients with HER2-positive, operable, locally advanced or inflammatory breast cancer.

The primary objectives of the trial were to compare the following parameters between trastuzumab SC and trastuzumab IV in the neoadjuvant setting:

- Serum trough concentrations (C_{trough}) observed pre-surgery; and
- Efficacy (pathological complete response).

The secondary objectives were to evaluate and compare additional efficacy indicators from the two arms including: total pathological complete response, overall response rate, time-to-response, event-free survival, overall survival, observed C_{trough} concentrations post-surgery, predicted C_{trough} concentrations pre-surgery and post-surgery, safety and tolerability.

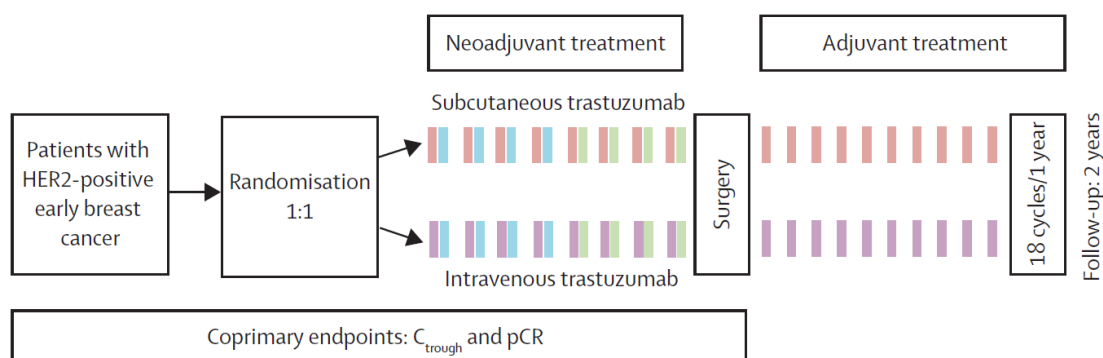
Table 1: Trials and associated reports presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
HannaH (BO22227)	Ismael G, Hegg R, Muehlbauer S, <i>et al.</i> Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial.	The Lancet Oncology. 2012;13(9): 869-78
	Jackisch C, Kim S-B, Semiglazov V, <i>et al.</i> Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study.	Annals of Oncology. 2014; Advance Access, November 17, 2014:1-22.
	HannaH CSR synopsis. Update Clinical Study Report – Protocol BO22227 - A phase III, randomized, open-label study to compare pharmacokinetics, efficacy and safety of subcutaneous trastuzumab with intravenous trastuzumab administered in women with HER2-positive early breast cancer.	Synopsis of research report 1057070. 2013:27-33

HER2 = human epidermal growth factor receptor; ID = identifier

6.5 The trial design for the HannaH trial is presented in Figure 1 below. A total of 596 patients were enrolled in the trial (299 patients in the trastuzumab IV arm and 297 patients in the trastuzumab SC arm). Patients were randomly assigned 1:1 to 8 cycles of preoperative neoadjuvant chemotherapy administered concurrently with trastuzumab every 3 weeks either intravenously (8 mg/kg loading dose, 6 mg/kg continuing dose) or subcutaneously (fixed dose of 600 mg). Chemotherapy consisted of 75 mg/m² docetaxel given every 21 days for 4 cycles followed by 4 cycles of 5-fluorouracil 500 mg/m², epirubicin 75 mg/m² and cyclophosphamide 500 mg/m² (FEC) given every 21 days. Following completion of chemotherapy (cycle 8), patients underwent surgery. After surgery patients received an additional 10 cycles of trastuzumab IV or trastuzumab SC as per randomisation to complete one year of treatment with trastuzumab.

Figure 1: Diagram of the HannaH trial design



- Trastuzumab subcutaneous 600 mg (5 mL) given every 3 weeks
- Trastuzumab intravenous 8 mg/kg loading dose; 6 mg/kg given every 3 weeks
- Docetaxel 75 mg/m²
- Fluorouracil (500 mg/m²), epirubicin (75 mg/m²), and cyclophosphamide (500 mg/m²) given every 3 weeks

Stratification factors were: breast-cancer type (operable versus locally advanced versus inflammatory) and oestrogen-receptor status (positive versus negative versus unknown)

C_{trough} = serum trough concentration; HER2 = human epidermal growth factor receptor; pCR = pathological complete response;

Comparative effectiveness

- 6.6 Results for the primary endpoint, C_{trough} pre-surgery (end of cycle 7, before cycle 8 dose) for trastuzumab SC (600 mg fixed dose) and trastuzumab IV (8 mg/kg loading dose, 6 mg/kg continuing dose) are shown in Table 2.

Table 2: Summary of data for the primary PK endpoint in the HannaH trial (per protocol population)

PK parameter	Trastuzumab IV (n = 235)	Trastuzumab SC (n = 234)
Mean observed serum C _{trough} (µg/mL)	57.8	78.7
Geometric mean (µg/mL; % coefficient of variation)	51.8 (52.5%)	69.0 (55.8%)
Geometric mean ratio (90% CI)	1.33 (1.24, 1.44)	

CI = confidence interval; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous

- 6.7 The submission concluded that trastuzumab SC was non-inferior to trastuzumab IV. The geometric mean ratio of C_{trough SC}/C_{trough IV} values was 1.33, with a corresponding lower limit of the two-sided 90% confidence interval (CI) of 1.24, which was above the pre-specified non-inferiority margin of 0.8.
- 6.8 The efficacy results, using pathological complete response as endpoint, are summarised in Table 3. Pathological complete response was defined as the absence of invasive neoplastic cells from the primary tumour in the breast after surgery.

Table 3: Summary of data for the primary pathological complete response endpoint in the Hannah trial (per protocol population)

	Trastuzumab IV (n = 263)	Trastuzumab SC (n = 260)
pCR (%)	107 (40.7%)	118 (45.4%)
95% CI for pCR	(34.7%, 46.9%)	(39.2%, 51.7%)
Difference in pCR rates	4.70	
Lower bound of the one-sided 97.5% CI for the difference in pCR rates	-4.0	

CI = confidence interval; IV = intravenous; pCR = pathological complete response; SC = subcutaneous

6.9 The submission stated that the pathological complete response confirmed the non-inferiority of trastuzumab SC compared to trastuzumab IV in patients with HER2-positive, operable, locally advanced or inflammatory breast cancer. The lower 95% CI boundary of the difference in pathological complete response rate between trastuzumab SC and trastuzumab IV was -4, which was greater than the inferiority margin of -12.5.

6.10 As this was a minor submission, the results were not independently evaluated.

Comparative harms

6.11 Comparisons of adverse events between trastuzumab SC and trastuzumab IV are shown in Table 4.

Table 4: Summary of safety data from the Hannah trial (safety population)

	Trastuzumab IV (n = 298)	Trastuzumab SC (n = 297)
Any adverse events	█████ (█████%)	█████ (█████%)
Grade ≥ 3 adverse events	█████ (█████%)	█████ (█████%)
Serious adverse events	█████ (█████%)	█████ (█████%)
Treatment related serious adverse events	█████ (█████%)	█████ (█████%)
Adverse events leading to treatment withdrawal	█████ (█████%)	█████ (█████%)
Adverse events leading to death	█████ (< █████%)	█████ (█████%)

IV = intravenous; SC = subcutaneous

6.12 There was no significant difference in the type or frequency of adverse events across the two treatment arms. The incidence of adverse events grade 3 and above was also comparable across both arms (█████% in the IV arm versus █████% in the SC arm).

6.13 Administration-related systemic reactions were observed more commonly for trastuzumab SC (47.8% in the SC arm versus 37.2% in the IV arm), with erythema and cough being the main contributors to the difference observed. In both study arms a large majority of adverse events (> 97%) were of grade 1 or 2 intensity.

6.14 As this was a minor submission, the results have not been independently evaluated.

Clinical claim

- 6.15 The submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of trastuzumab SC (600 mg fixed dose) compared with trastuzumab IV (8 mg/kg loading dose, 6 mg/kg continuing dose).
- 6.16 The PBAC noted that the SC formulation of trastuzumab is quite different from the IV formulation because SC contains the recombinant human hyaluronidase permeation enhancer.
- 6.17 The PBAC noted that HannaH did not represent the range of circumstances of potential use of trastuzumab SC in clinical practice. For instance:
- no data was presented on the safety or efficacy of patients switching between IV and SC trastuzumab.(or back and forth between the formulations),
 - the chemotherapy partners used in practice would be broader than in the trial, and
 - the trial only included patients who were eligible for neoadjuvant (followed by adjuvant) treatment. .
- 6.18 In addition, the submission did not provide evidence of treatment with trastuzumab SC in patients with metastatic breast cancer treated, either with or without pertuzumab. PBAC also noted that the duration of follow-up of patients treated with SC trastuzumab was considerably less than the long term follow-up of patients exposed to IV trastuzumab.
- 6.19 The Pre-PBAC Response noted that there is a current open-label, multicentre, phase IIIb study (SAPPHIRE) investigating the combination of pertuzumab with SC trastuzumab and a taxane in patients with HER2-positive metastatic breast cancer. The study will assess the safety, tolerability, and efficacy of the treatment and has an expected completion date of early 2017. The Pre-PBAC Response provided an abstract of interim analysis of 50 Australian patients that observed that the safety profile was consistent with trials using trastuzumab with and without pertuzumab.
- 6.20 The Pre-PBAC Response also noted that there is also another ongoing study in France, specifically examining trastuzumab SC in metastatic breast cancer, though no details of the study were provided.

Economic analysis

- 6.21 The submission presented a cost-minimisation analysis and sought an equivalent ex-manufacturer price for the fixed-dose trastuzumab SC formulation (600 mg) to the current trastuzumab IV formulation. For the IV formulation, cost calculations are based on a dose of 6 mg/kg and local demographic data on weights of Australian patients, and not based on the treatment course in the HannaH trial (8 mg/kg loading dose, 6 mg/kg continuing dose).
- A dose of [REDACTED] mg: 6 mg/kg and mean body weights of [REDACTED] kg for patients with early breast cancer (n=[REDACTED]; range [REDACTED] kg, Tandem Cancer Audit Program LA/EBC sample, Ipsos 2014), and

- A dose of ■■■ mg: 6 mg/kg and mean body weights of ■■■ kg for patients with metastatic breast cancer (Source: Ipsos Oncology Monitor 2012, Attachment to Pertuzumab submission, March 2014 PBAC meeting).
- 6.22 The submission noted that a special pricing arrangement had been proposed for the PBS listing of trastuzumab in the metastatic setting, whereby the effective subsidy price proposed for that setting is less than the current PBS price for trastuzumab. The submission acknowledged this price may require updating to reflect the actual agreed effective price.
- 6.23 The dose of trastuzumab IV for calculating an equivalent ex-manufacturer price was rounded from the weight based dose to 450 mg (complete vials: 1 x 150 mg, 5 x 60 mg).
- 6.24 The calculated DPMQ for trastuzumab SC 600 mg/5 mL does not include an infusion administration cost. Trastuzumab IV is provided under the Efficient Funding of Chemotherapy – Section 100 arrangements; whereas trastuzumab SC will be listed under the General Schedule with a wholesaler mark-up and other applicable fees applied. In addition, a special pricing arrangement, with rebate, will be needed to accommodate the lower price for trastuzumab in metastatic breast cancer (see Table 5).

Table 5: Cost-minimisation analysis calculations for trastuzumab SC 600 mg/5 mL

	Early and locally advanced breast cancer		Metastatic breast cancer	
	IV	SC	IV	SC
Current ex-manufacturer price				
60 mg	\$■■■	N/A	\$■■■	N/A
150 mg	\$■■■	N/A	\$■■■	N/A
600 mg	N/A	Requested	N/A	Requested
Dose (for mean body weight)	■■■ mg	600 mg	■■■ mg	600 mg
Number of vials (rounded up to complete vials)	1 x 150 mg, 5 x 60 mg	1	1 x 150 mg, 5 x 60 mg	1
Ex-manufacturer price	\$■■■	\$■■■	\$■■■	\$■■■
DPMQ public	N/A	\$■■■	N/A	\$■■■
DPMQ private	N/A	\$■■■	N/A	\$■■■

Source: Adapted from Table 3.2, p11 of the submission; and from sheet "Pricing Request" from "Trastuzumab SC financials.xlsx"

DPMQ = Dispensed price for maximum quantity; IV = intravenous; N/A = not applicable; SC = subcutaneous

Estimated PBS usage and financial implications

- 6.25 The submission states that Australian clinicians have limited experience with the trastuzumab SC formulation and given the high acceptability of the existing IV formulation for the last 10 years, the trastuzumab SC formulation will have a modest level of adoption with a peak market share of ■■■% in early, locally advanced or metastatic breast cancer.
- 6.26 The submission claims the listing of trastuzumab SC would generate savings due to reduced drug acquisition costs and a reduction in MBS item claims (for example, 13915, infusion of not more than 1 hour duration) compared to trastuzumab IV, as there is no MBS item code available for the administration of trastuzumab SC.

However, its listing as a general schedule item, with an 11.1% wholesaler mark-up and applicable fees applied, would result in a net increase in total costs for the PBS and a net cost to Government. The costs of listing trastuzumab SC on the PBS are summarised in Table 6, as well as the expected prescription numbers.

- 6.27 The submission states that ‘No change in MBS codes is assumed when trastuzumab SC is given in combination with concomitant IV chemotherapies as these still attract an MBS item for IV administration (assumed for neoadjuvant therapy [8 cycles as per Hannah protocol] and all metastatic breast cancer [uncertain proportion of cycles without concomitant chemotherapy]).’ This assumption may include patients with metastatic breast cancer receiving maintenance therapy with pertuzumab and trastuzumab (without chemotherapy), as pertuzumab is administered as an IV infusion. This scenario was not explicitly stated in the submission.

Table 6: Estimated prescriptions numbers and overall net cost to Commonwealth Government of trastuzumab SC 600 mg/5 mL

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Early breast cancer and locally advanced breast cancer						
Market share of SC after listing	%	%	%	%	%	%
Number of scripts for SC						
Number of scripts for IV						
Metastatic breast cancer						
Market share of SC after listing	%	%	%	%	%	%
Number of scripts for SC						
Number of scripts for IV						
Overall all net costs (early breast cancer, locally advanced breast cancer and metastatic breast cancer)						
Overall net cost to the PBS	\$	\$	\$	\$	\$	\$
Overall net cost to the RPBS	\$	\$	\$	\$	\$	\$
Overall net cost for MBS	-\$	-\$	-\$	-\$	-\$	-\$
Overall Net cost to Government	\$	\$	\$	\$	\$	\$

IV = intravenous; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SC = subcutaneous

- 6.28 The redacted table above shows that the minor submission estimated there would be a small net increase in the costs to the PBS and the Commonwealth Government of less than \$10 million in Year 1 increasing to less than \$10 million in Year 6 if trastuzumab SC were to be listed on the PBS. The net cost to Government over 6 years would be \$10 - \$20 million. The submission assumed all trastuzumab SC prescriptions are dispensed as general schedule items and attract the 11.1% wholesaler mark-up and other applicable fees.
- 6.29 At year 6, the estimated number of scripts was 10,000 - 50,000 (early, locally advanced and metastatic breast cancer) and the net cost to the PBS/RPBS would be less than \$10 million.
- 6.30 The PBAC noted that there was uncertainty in the net cost to the Government, due to the:
- conservative calculation of the cost-minimised drug cost of forms requiring different modes of administration and not including the IV loading dose.
 - the number of patients who may switch from trastuzumab IV to trastuzumab SC is unknown.

- the proportion of General Schedule and Section 100 prescribing is unknown.

However, the PBAC considered that the listing should only proceed if the cost to Government, based on the usage estimates presented in the submission, was at worst, neutral. The PBAC further recommended that usage be monitored and the price of trastuzumab SC be further reduced if the usage of this form was higher than estimated by the submission.

- 6.31 The PBAC noted that the risk sharing arrangements (RSA) for early-line breast cancer were not volume or form dependent, while a single cap for all trastuzumab IV use was the basis of the risk sharing arrangements for the treatment of metastatic breast cancer. The Pre-PBAC response stated that the sponsor is willing to work with the Department as appropriate to amend the existing RSA for trastuzumab in metastatic breast cancer in order to include government expenditure associated with trastuzumab SC. The PBAC recalled that providing budget certainty through a RSA implemented as intended was an important consideration in recommending trastuzumab, pertuzumab and trastuzumab emtansine for the treatment of metastatic breast cancer at the November 2014 PBAC meeting. The PBAC considered it is appropriate that trastuzumab SC to be included in the existing RSA for metastatic breast cancer maintaining the existing financial caps for the treatment of metastatic breast cancer in a manner than can be implemented by the Department.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule and Schedule 100 Efficient Funding of Chemotherapy ('Related Pharmaceutical Benefits') listing of trastuzumab SC, for patients with locally advanced human epidermal growth factor receptor 2 (HER2) positive breast cancer, early HER2 positive breast cancer and metastatic (Stage IV) HER2-positive breast cancer.
- 7.2 The PBAC was satisfied that trastuzumab SC is safe and effective in treatment-naïve patients initiating on this form of trastuzumab; that there is no evidence of significant differences in clinical effectiveness or safety compared with the IV form, and there is no evidence that identifies populations in whom the risks of using the SC form of trastuzumab are disproportionately high. The PBAC was concerned that only very limited clinical efficacy and safety data was provided in support of switching between trastuzumab SC and its IV form, as this is likely to occur in clinical practice. In addition, the chemotherapy partners in practice will be broader than those for which evidence was provided, and trial evidence was not available for the metastatic breast cancer setting.
- 7.3 The PBAC concluded that it could not be completely assured of the efficacy and safety of trastuzumab SC in clinical practice. However the PBAC considered that, on balance it was appropriate to recommend trastuzumab SC be listed on the PBS and that patients with breast cancer should be able to access trastuzumab SC via the PBS in the same way as the currently listed trastuzumab IV and without any restriction on switching between the different forms. The recommendation was made on the basis that the listing should, at worst, be cost-neutral for government.

- 7.4 The PBAC noted the cost-minimisation in the submission was based on the drug cost only and that the equi-effective dose for this calculation was trastuzumab SC (600 mg fixed dose) and trastuzumab IV (450 mg, weight based dose). The protocol of the primary clinical evidence, the HannaH trial included a loading IV dose that matched how the two forms would be used in practice.
- 7.5 The PBAC welcomed the input provided via the Consumer Comments facility describing the range of benefits of treatment with trastuzumab SC. The PBAC noted the PrefHer study in the submission, but the magnitude of patient convenience reported in the study was not evaluated in the context of the minor submission. The PBAC accepted that trastuzumab SC may offer a convenient alternative to the IV formulation.
- 7.6 The PBAC accepted trastuzumab IV as the appropriate comparator.
- 7.7 The PBAC accepted trastuzumab SC is non-inferior in efficacy and safety compared with trastuzumab IV when an entire course of treatment is administered to a patient with early breast cancer either subcutaneously or intravenously, as was done in the HannaH trial.
- 7.8 However the PBAC considered that the HannaH clinical trial's approach of exclusively using one route of administration for trastuzumab is unlikely to be followed in clinical practice. In clinical practice patients may switch between the intravenous and subcutaneous forms of trastuzumab on one, or multiple, occasions. However no data has been provided in the HannaH trial to enable an assessment of the efficacy or safety of switching. Though the submission provided information on the PrefHer study to support the claim that the SC formulation was a more convenient alternative to IV administration, the PBAC noted that secondary endpoints in this trial included safety and tolerability, event-free survival (time to local, regional, or distant recurrence, contralateral breast cancer, or death from any cause), immunogenicity (anti-trastuzumab and anti-rHuPH20 antibodies). The PBAC noted in the PrefHer study that approximately 83% of patients were treated with trastuzumab IV prior to enrolment and that all patients were treated with 4 cycles of one form of trastuzumab and then switched to the other form of the drug for a further 14 cycles. The submission stated trastuzumab SC was well tolerated in the PrefHer study with no new safety signals identified compared with the known profile of trastuzumab IV. In the pooled analysis (both cohorts), the incidence of serious adverse events was low and comparable in both arms (<1% in both IV and SC arms). The PBAC noted that no data on event-free survival and immunogenicity were provided in the submission.
- 7.9 The limited switching data is particularly important because:
- the new SC formulation is substantively different from the intravenous formulation – specifically because it contains a recombinant human hyaluronidase permeation enhancer;
 - Immunogenicity can be different for biological drugs such as trastuzumab when they are given via the SC route versus the intravenous route; and
 - the proposed use of the new trastuzumab SC is in a patient population for many of whom the goal is cure and long term safety is important.

Notwithstanding that the IV and SC forms of trastuzumab are not suitable for substitution at the pharmacist level (because the dosing is different), the same considerations equally apply to switching at the prescriber level.

- 7.10 The PBAC recalled that it had recommended a subcutaneous form of rituximab at its November 2014 meeting on the basis of similar clinical data to that presented in this submission for trastuzumab SC. Since then, a number of consumer and clinician groups have raised concerns regarding moving patients between a reference biological drug and a biosimilar drug. Although the groups hadn't said so, the PBAC considered the concerns of these groups should equally apply to moving between the IV and SC routes of administration of the same brand of a biological drug, where switching is driven by the prescriber rather than the pharmacist.
- 7.11 In addition, the chemotherapy partners in practice will be broader than in the HannahH trial, and the HannahH trial was only conducted in the neoadjuvant then adjuvant setting in early breast cancer and not in the metastatic breast cancer setting.
- 7.12 The PBAC noted that the submission had estimated that listing of trastuzumab SC would have a cost to the Government, but actual cost would depend on the uptake rate of this form of drug and the setting in which it was prescribed. The PBAC considered that the risk to the Commonwealth may be mitigated by the inclusion of the SC form in the RSA for the metastatic breast cancer indication. The PBAC also noted that there may be additional out-of-pocket cost to patients who seek treatment with the SC form.
- 7.13 The PBAC considered that the listing should only proceed if the cost to Government, based on the usage estimates presented in the submission, was at worst neutral. The PBAC further recommended that usage be monitored and the price of trastuzumab SC be further reduced if the usage of this form was higher than estimated by the submission.
- 7.14 The PBAC noted that trastuzumab IV was recommended at the same meeting for the treatment of metastatic (Stage IV) HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction. As the current TGA registration for the SC form does not include this indication, it was appropriate that listing of trastuzumab SC at time does not include treatment of metastatic (Stage IV) HER2 positive adenocarcinoma of the stomach or gastro-oesophageal junction.
- 7.15 The PBAC advised that trastuzumab SC should be treated as interchangeable on an individual patient basis with trastuzumab IV.
- 7.16 The PBAC advised that trastuzumab is not suitable for prescribing by nurse practitioners.
- 7.17 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.18 The PBAC noted that this submission is not eligible for an Independent Review, because it received a positive recommendation.

Outcome:

Recommended.

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
TRASTUZUMAB Solution for subcutaneous injection 600 mg/5 mL	600 mg	0	Herceptin® Roche
Category / Program:	GENERAL – General Schedule (Code GE) Section 100 EFC Public Hospitals (Related Pharmaceutical Benefits) Section 100 EFC Private Hospital/Private Clinic (Related Pharmaceutical Benefits)		
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		
Episodicity:			
Condition:			
PBS Indication:	1.HER2-positive early breast cancer 2.Locally advanced HER2-positive breast cancer 3. Metastatic (Stage IV) HER2 positive breast cancer		
Treatment phase:	Initial treatment (3 weekly regimen) (indication 1 and 2) Initial treatment (indication 3)		
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing		

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
TRASTUZUMAB Solution for subcutaneous injection 600 mg/5 mL	600 mg	3	Herceptin® Roche
Category / Program:	GENERAL – General Schedule (Code GE) Section 100 EFC Public Hospitals (Related Pharmaceutical Benefits) Section 100 EFC Private Hospital/Private Clinic (Related Pharmaceutical Benefits)		
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		
PBS Indication:	1.HER2-positive early breast cancer 2.Locally advanced HER2-positive breast cancer 3. Metastatic (Stage IV) HER2 positive breast cancer 4. HER2 positive breast cancer		
Treatment phase:	continuing treatment (3 weekly regimen) (indication 1 and 2) continuing treatment (indication 3) Grandfathering treatment (indication 4)		
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone		

Restriction wording as current trastuzumab listings (HER2-positive early breast cancer. Locally advanced HER2-positive breast cancer, Metastatic (Stage IV) HER2 positive breast cancer and HER2 positive breast cancer (grandfathering treatment).

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 is pleased by the PBAC's positive recommendation for trastuzumab SC and looks forward to working with government to finalise its PBS listing as promptly as possible.