

Medicines for the treatment of HER2 positive metastatic breast cancer: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

February 2018

Abstract

Purpose

To compare the predicted and actual utilisation of trastuzumab, trastuzumab emtansine (T-DM1) and pertuzumab for the treatment of human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer.

Current PBS restriction (abridged)

Metastatic (Stage IV) HER2 positive breast cancer. The details of the restrictions vary across the three medicines. See the “Restriction” section on page 6 for details.

Key Findings

- Larger numbers of patients used pertuzumab and trastuzumab than expected in both the first two years.
- The use of pertuzumab was for a greater number of cycles than anticipated in the submission. █% of patients had more than █ cycles of treatment (█).
- Lower numbers of patients used T-DM1 than predicted. A contributing factor could be patients staying on pertuzumab longer than expected and so not progressing to T-DM1.

Purpose of analysis

To compare the predicted and actual utilisation of trastuzumab, trastuzumab emtansine (T-DM1) and pertuzumab for the treatment of HER2 positive metastatic breast cancer.

Information on lapatinib is included where appropriate. Lapatinib was reviewed by DUSC in February 2010.

Background

Pharmacology

Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2).

Trastuzumab inhibits the proliferation of human tumour cells that overexpress HER2.

Trastuzumab emtansine is a HER2 targeted antibody-drug conjugate that contains trastuzumab covalently linked to the cytotoxic agent emtansine (DM1).

Pertuzumab is a recombinant humanised monoclonal antibody. It binds to HER2 using a different site to trastuzumab.

Therapeutic Goods Administration (TGA) approved indication¹

Trastuzumab (Herceptin®) is approved for the treatment of:

- Early breast cancer expressing HER2 in association with chemotherapy and, if applicable, radiotherapy.
- Locally advanced breast cancer expressing HER2 in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab.
- Metastatic breast cancer expressing HER2 as:
 - monotherapy where patients have received one or more chemotherapy regimens, or
 - in combination with taxanes in patients who have not received chemotherapy for metastatic disease, or
 - in combination with an aromatase inhibitor for post-menopausal patients with hormone-receptor positive metastatic breast cancer.
- Advanced gastric cancer in combination with cisplatin and either 5-FU or capecitabine.

¹ Herceptin Product Information updated 16 June 2016. Available on the ARTG at www.tga.gov.au accessed 27 November 2017.

Trastuzumab is available as a 150 mg vial and 60 mg vial for intravenous infusion. It is also available as a 600 mg subcutaneous injection.

Clinical practice for prescribing trastuzumab for metastatic breast cancer (MBC) has shifted since the inception of the Herceptin Program in 2001. In particular, the chemotherapy administered with trastuzumab is not always a taxane. As taxanes are now commonly administered in the adjuvant setting, trastuzumab is sometimes given in combination with alternate chemotherapy agents such as vinorelbine when a patient progresses to metastatic disease.²

The PBAC considered evidence for a number of additional regimens to those listed in the approved product indication.³ Refer to the section on relevant aspects of consideration by PBAC.

Trastuzumab emtansine⁴ (T-DM1) is approved for treatment of patients with HER2 positive metastatic breast cancer who previously received trastuzumab and a taxane either separately or in combination. Patients should have either received prior therapy for metastatic disease or developed disease recurrent during or within six months of completing adjuvant therapy.

Trastuzumab emtansine is available as a 100 mg vial.

Pertuzumab (Perjeta®) is approved, in combination with trastuzumab and chemotherapy in neoadjuvant treatment of patients with inflammatory or locally advanced HER2 positive breast cancer and in patients with metastatic disease who have not had prior anti-HER2 therapy or chemotherapy for metastatic disease.⁵

Pertuzumab is supplied in 420 mg vials.

Lapatinib (Tykerb®) is approved for the treatment in combination with capecitabine in patients with advanced metastatic breast cancer whose tumours overexpress HER2 and have progressed after treatment with an anthracycline, a taxane and trastuzumab.

Lapatinib is supplied as 250mg tablets.

Dosage and administration

In breast cancer trastuzumab can be administered as a three-weekly infusion with an initial loading dose of 8 mg/kg following by 6 mg/kg every three weeks. Alternatively there is a weekly schedule with a loading dose of 4 mg/kg and weekly doses of 2 mg/kg. Trastuzumab can also be administered as a 600 mg subcutaneous injection every three weeks (no loading dose required).

² Pearson SA, Ringland CL and Ward RL. Trastuzumab and metastatic breast cancer: trastuzumab use in Australia – monitoring the effect of an expensive medicine access program. *J Clin Oncol* 25:3688-3693 (2007).

³ Herceptin Program Review Item 9.1 PBAC meeting November 2008

⁴ Kadcyla (trastuzumab emtansine) product information. Last update 11 February 2016. Available at tga.gov.au, accessed 1 December 2017.

⁵ Perjeta (pertuzumab) product information. Last update 31 August 2016. Available at tga.gov.au, accessed 1 December 2017

Where trastuzumab is used with pertuzumab the regimen is three-weekly infusions. The dose of pertuzumab is 840 mg loading dose plus 8 mg/kg trastuzumab then 420 mg pertuzumab plus 6 mg/kg trastuzumab every three weeks.

Patients with early or locally advanced breast cancer should be treated for one year or until disease recurrence, whichever occurs first.

Patients with metastatic breast cancer should be treated until progression of the disease (product information for Herceptin). In Australian practice some patients with metastatic breast cancer continue to be treated beyond disease progression. This view was supported by input from clinicians and patients to the PBAC (May 2014 Stakeholder meeting).

Trastuzumab emtansine is administered at a dose of 3.6 mg/kg via IV infusion every three weeks until disease progression or unacceptable toxicity.

PBS listing details (as at 1 November 2017)

Table 1: PBS items for trastuzumab, trastuzumab emtansine (T-DM1) and pertuzumab listed for the treatment of HER2 positive breast cancer (various stages).

Drug Name, Form and Strength	Item code	Stage of Breast Cancer	
TRATUZUMAB			
Powder for I.V. infusion 60 mg	4632T	Early or locally advanced	
	4639E		
	4650R		
	4703M		
	7264H		
	7265J		
	7266K		
	7267L		
	10381J	Metastatic, Grandfathered	
	10423N		
	10383L	Metastatic	
	10391X		
	10401K		
	10402L		
Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	10682F	Early or locally advanced	
	10721G		
	10743K		
	10744L		
	10825R	Metastatic, Grandfathered	
	10829Y		
	10798H	Metastatic	
	10803N		
	10811B		
	10817H		
TRASTUZUMAB EMTANSINE			
Powder for I.V. infusion 100 mg	10281D	Metastatic or Metastatic, Grandfathered	
	10282E		
PERTUZUMAB			
Solution for I.V. infusion 420 mg in 14 mL	10268K	Metastatic, Grandfathered	
	10309N		
		10267J	Metastatic
		10308M	
	10333W		
	10334X		
LAPATINIB			
Tablets 250mg	9148L	Metastatic	

Some item codes cover use for different stages of breast cancer. For example, item 4632T can be used for early or locally advanced stages. The stage of breast cancer assigned to a prescription can be determined from the authority approval restriction code (See Appendix A).

Restriction

Trastuzumab, pertuzumab, T-DM1 and lapatinib are Authority Required PBS medicines. The initiation application must be made in writing but continuing treatment can be approved by phone.

This report will mainly have regard to MBC. The restriction wording (as at 1/11/2017) for initial treatment with trastuzumab for MBC was:

Metastatic (Stage IV) HER2 positive breast cancer

Treatment Phase: Initial treatment

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.*

The restriction wording (as at 1/11/2017) for initial treatment with T-DM1 for MBC was:

Metastatic (Stage IV) HER2 positive breast cancer

Treatment Phase: Initial treatment

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 condition must have progressed following treatment with pertuzumab and trastuzumab in combination; OR*

** The condition must have progressed during or within 6 months of completing adjuvant therapy with trastuzumab, AND*

** Patient must have a WHO performance status of 0 or 1, AND*

** The treatment must be as monotherapy, 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.*

The restriction wording (as at 1/11/2017) for initial treatment with pertuzumab for MBC was:

Metastatic (Stage IV) HER2 positive breast cancer Treatment Phase: Initial treatment 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*

- * Patient must have a WHO performance status of 0 or 1, AND
- * Patient must not have received prior anti-HER2 therapy for this condition, AND
- * Patient must not have received prior chemotherapy for this condition, AND
- * The treatment must be in combination with trastuzumab and a taxane, 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.

The restriction wording (as at 11/2017) for initial treatment with lapatinib for MBC was:

Metastatic (Stage IV) HER2 positive breast cancer

Treatment Phase: Initial treatment

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 be in combination with capecitabine, AND*
 - *Patient must have received prior therapy with a taxane for at least 3 cycles; OR*
 - *Patient must have developed intolerance to treatment with a taxane of a severity necessitating permanent treatment withdrawal,*

AND

- *The condition must have progressed following treatment with pertuzumab and trastuzumab in combination, AND*
- *The treatment must be the sole PBS-subsidised anti-HER2 therapy for this condition, 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.*

For more details of the PBS listing refer to the Appendices A and B and the PBS website. Dates of PBS listing of all drugs for the treatment of breast cancer can be found in Attachment 1.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

Table 2: Summary of PBAC consideration of trastuzumab, pertuzumab and trastuzumab emtansine (T-DM1)

PBAC meeting(s)	
September 2000 / March 2001	Consideration of trastuzumab for HER2+ metastatic breast cancer. PBAC concludes that trastuzumab provides additional benefit in extending progression free survival (PFS) but was not acceptably cost effective.
December 2001	Government implements the Herceptin Program providing access to trastuzumab 150 mg.
2004	First Government review of Herceptin Program.
July 2006	Second Government review of Herceptin Program. Advice from PBAC provided to the Minister. PBAC recommends listing trastuzumab in early breast cancer.
1 October 2006	Trastuzumab listed on PBS for early breast cancer
July 2007	PBAC recommends lapatinib for HER2+ metastatic breast cancer
1 December 2007	Lapatinib listed on PBS for metastatic breast cancer (MBC)
November 2008	Third review of Herceptin Program. PBAC advised the Minister that trastuzumab was not acceptably cost-effective at the price offered.
July 2010	PBAC recommended listing of trastuzumab 60 mg injection in early breast cancer.
November 2014	PBAC recommended: Pertuzumab plus trastuzumab plus taxane in MBC , Trastuzumab 150 mg and 60 mg plus taxane or vinorelbine in MBC, Trastuzumab 150 mg and 60 mg as monotherapy in MBC, Trastuzumab-emtansine in MBC after disease progression. Listed on the PBS on 1 July 2015
July 2015	PBAC recommended: Trastuzumab subcutaneous 600 mg/5 mL for the same PBS early and metastatic breast cancer restrictions as trastuzumab infusions.

Comparative clinical effectiveness

Trastuzumab

The PBAC (September 2000) considered that there was good evidence to support the effectiveness of trastuzumab in combination with taxanes in MBC. This remained the recommendation of the PBAC (November 2008, November 2014). The comparative clinical effectiveness of monotherapy was uncertain (September 2001, November 2008). Additional evidence was provided by Roche for consideration in November 2014.

In the November 2008 review of trastuzumab in MBC (Herceptin Program), the PBAC considered evidence for additional therapies to those considered in 2001. The PBAC concluded:

- *Trastuzumab in combination with aromatase inhibitors*, in oestrogen receptor positive patients, was more effective but associated with greater toxicity than aromatase inhibitors alone in first and second line treatment.
- *Trastuzumab plus vinorelbine* showed an increasing trend supporting greater efficacy compared to vinorelbine alone. The evidence was difficult to interpret owing to biases associated with single arm studies and confounding. Studies comparing trastuzumab plus vinorelbine with trastuzumab plus taxane in first line treatment demonstrated equal efficacy with different toxicity profiles. This combination is not approved in the product information.
- *Trastuzumab plus taxanes plus another chemotherapy*. The PBAC found it could not be certain of additional benefit but noted there was greater toxicity. This combination is not approved in the product information.
- *Trastuzumab as monotherapy* used beyond disease progression shows uncertain evidence of clinical benefit. Use beyond disease progression is not approved in the product information.
- There was no evidence available to support clinical benefit of trastuzumab in patients who have been treated with adjuvant trastuzumab in early breast cancer who then relapsed and presented with MBC. The lack of evidence for these patients is noted in the product information.

In November 2014 the PBAC considered a further request for trastuzumab to be listed on the PBS for MBC. The committee noted its conclusions from previous considerations of the evidence (November 2008). The PBAC considered new evidence of clinical benefit in patients who had disease progression and where trastuzumab was being used in second and subsequent lines of treatment.

The PBAC considered that the results of the M77001 study provided evidence that trastuzumab plus docetaxel in first line therapy was associated with patients having a longer time before their disease worsened (time to progression, TTP) and longer time to death (overall survival) compared to docetaxel alone.

The most reliable evidence for use of trastuzumab in second and later lines was provided by study GBG 26. The evidence from this study showed that trastuzumab plus capecitabine was associated with a longer time until the disease worsened compared to capecitabine alone. The study was of poor quality and the result measuring survival was not robust. PBAC accepted that more robust evidence was unlikely to be obtained.

The PBAC noted the clinical use of HER2 blockade until death with and without continuous chemotherapy for a significant number of patients in practice. This affects treatment costs and exposes patients to risk of adverse events without good evidence to support this practice.

Pertuzumab

Pertuzumab used in combination with trastuzumab plus docetaxel was superior to trastuzumab plus docetaxel alone in increasing the time patients' tumours did not worsen (progression free survival). The combination was slightly worse in terms of comparative safety over trastuzumab plus docetaxel alone, as there were more adverse events in patients treated

with the combination. The CLEOPATRA trial showed a median of 18.7 months progression free survival (95%CI 17, 22) when patients were treated with pertuzumab plus trastuzumab plus docetaxel compared to 12.4 (95%CI 10, 14) with trastuzumab plus docetaxel alone providing an incremental gain of 6.3 months. The updated 2014 results for median overall survival showed an incremental gain of 15.7 months. The population enrolled in the CLEOPATRA trial had at least 12 months between completion of treatment for early breast cancer and progression of disease to metastatic or unresectable locally advanced disease.

One course of pertuzumab is subsidised per patient lifetime.

Trastuzumab emtansine (T-DM1)

T-DM1 was superior in terms of time patients' tumours did not worsen (progression free survival) and survival compared to lapatinib plus capecitabine. The EMILIA trial showed an incremental gain of 5.8 months in median overall survival and 3.2 months in median progression free survival. The PBAC also noted that there were more adverse events in patients receiving T-DM1.

However this gain was not convincingly demonstrated in patients who had prior treatment with pertuzumab plus trastuzumab and therefore there was some uncertainty about the magnitude of the benefit that would be seen once pertuzumab plus trastuzumab was standard therapy for first line MBC treatment. There was some use of pertuzumab in patients enrolling in the EMILIA trial but the proportion was too small for any meaningful conclusion about differences in benefit.

One course of T-DM1 is subsidised per patient lifetime.

Cost-effectiveness

Trastuzumab

Trastuzumab was initially not acceptably cost-effective at the price proposed for either combination therapy with taxanes or monotherapy (September 2000 and March 2001 PBAC meetings).

A new model was considered by PBAC in November 2008. The PBAC considered that the Markov model used to assess the cost-effectiveness of trastuzumab in MBC was robust. Any assumptions that might favour trastuzumab and underestimate the incremental cost-effectiveness ratio (ICER) (e.g. that there was no use of drug beyond progression and that there were no costs associated with progression) were likely to be balanced by assumptions that bias the ICER against trastuzumab (e.g. the likelihood that the survival advantage in first line setting was underestimated because of cross over and the poor patient selection resulting from inaccurate testing for HER2 when some of the studies were designed). Overall the committee noted that if the price of trastuzumab was reduced by a substantial amount the ICER would fall into a range which would make it acceptable for PBS subsidy.

The models presented in the November 2014 submission included the use of trastuzumab in first-line therapy and in multiple-lines of therapy. The price of trastuzumab was reduced.

The PBAC concluded that the ICER for first line trastuzumab remains high but was more certain than the ICER for second line. The model in this submission was likely to underestimate the ICER/LYG for multiple lines of treatment due to likely biases in the clinical evidence, not translating the incremental benefit into QALYs gained, excluding the cost and disutilities associated with adverse events and excluding costs of some chemotherapies and retesting of HER2 status. Overall the model was very sensitive to the price of trastuzumab.

Pertuzumab

The PBAC considered the economic model to be reasonably reliable but noted that post progression costs in particular favoured pertuzumab.

[REDACTED]

Trastuzumab emtansine (T-DM1)

The PBAC accepted the model as reasonably reliable but noted that the assumptions and inputs for a number of parameters favour T-DM1 and lead to uncertainty in concluding cost effectiveness. These included [REDACTED] % of the survival gain was after disease progression, an imbalance in HER2 therapy across the treatments being compared in the model, and the way costs of disease progression are attributed.

[REDACTED]

Access to each product (restriction)

The PBAC (November 2014) reviewed the restrictions for all three medicines. The committee was concerned to ensure that the restrictions reflected current evidence and legitimised clinical practice by allowing use of trastuzumab beyond progression and a range of partner chemotherapy options, with the exception of nab-paclitaxel. The PBAC noted that the restriction should ensure that patients currently accessing trastuzumab on the Herceptin Program would continue to have access to trastuzumab through the PBS. Adjustments to the lapatinib restriction followed finalisation of these restrictions.

Approach taken to estimate utilisation

The submissions to the PBAC from Roche for trastuzumab, T-DM1 and pertuzumab for MBC were considered by DUSC at its October 2014 meeting.

The submissions used Herceptin Program data to estimate patient numbers and current expenditure. The Herceptin Program was implemented from 1 December 2001 by the government to provide access to trastuzumab 150mg vials for treatment of HER2 expressing (HER2+) MBC. This program was managed separately to the PBS.

The submissions used the Herceptin Program patient numbers as a base for eligible patients. The submission for pertuzumab estimated 95% of patients diagnosed with HER2+ MBC currently commence first line treatment with trastuzumab with 5% of patients contraindicated to trastuzumab (Section E pertuzumab submission pp5-6). DUSC agreed that the Herceptin Program patient numbers were a good basis for estimates of eligible patients. In spite of there being no published data on incidence of HER2+ MBC, new enrollees to the Herceptin Program were likely to account for almost all patients diagnosed with the condition. The submissions assumed 83% of patients would commence pertuzumab while the remaining 17% would use trastuzumab+taxane therapy in first line MBC treatment. DUSC considered that pertuzumab uptake of 83% was underestimated given the substantial survival benefits demonstrated in the CLEOPATRA trial. It was considered that 95% uptake would be more likely. The committee considered 100% uptake is possible given that there are no significant contraindications to pertuzumab (aside from hypersensitivity reactions). DUSC revised the base case estimates, increasing the uptake of pertuzumab from 83% to 95%. This was subsequently applied to the estimates accepted by Roche and the government.

The estimates of patient use and cost assume [REDACTED] % of patients will be alive two years after starting first line treatment with pertuzumab plus trastuzumab. Using the results of the CLEOPATRA trial the estimates assumed [REDACTED] % of patients will have worsening or progressed disease after two years. All of these patients will be eligible to use T-DM1 after disease progression (second-line treatment). DUSC considered that the number of people with disease progression and therefore eligible for T-DM1 may be underestimated in the estimates for the earlier years (years 1 and 2) of listing. In the CLEOPATRA trial almost 50% of patients in the comparator arm (trastuzumab only) had experienced disease progression at 12 months. By applying two years for PFS rather than one year the number of eligible second line treatment patients in year 1 and 2 would not be adequately accounted for. DUSC considered that in the later years (years 3 and 4), applying the results from CLEOPATRA was appropriate and likely to be more accurate as all patients will have had the opportunity to use trastuzumab plus pertuzumab.

The PBAC noted that a large proportion of the cost of T-DM1 in the estimates of use was contributed by use of T-DM1 in patients as third line therapy in the first two years of listing. Third line therapy with T-DM1 was assumed to stop after this time and third line therapy would be with trastuzumab.

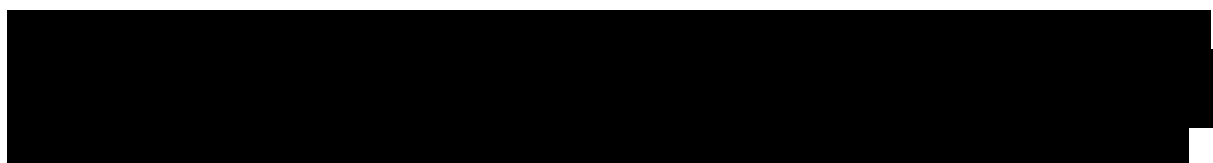
The trastuzumab submission assumed third and later line trastuzumab use would remain at current levels. DUSC considered this to be uncertain. The survival benefits of pertuzumab and T-DM1 would increase the prevalent population with metastatic breast cancer; however it was difficult to say whether this would increase use of trastuzumab in later lines of therapy given the availability of T-DM1.

The PBAC also considered that the cost offsets proposed for reduced use of taxanes were overestimated.

Overall DUSC considered the estimates presented in the submission to be underestimated. The main issues were:

- The uptake of pertuzumab is likely to be higher than the base case (83%). Given the substantial survival benefit in the CLEOPATRA trial, uptake may be up to 100%. *This was later adjusted to be 95%*
- The financial estimates may not adequately account for increased prevalence of HER2 positive metastatic breast cancer. Due to the survival gains from the newer treatments (trastuzumab plus pertuzumab first line and T-DM1 second line which both have shown an increase in median PFS) there is likely to be a larger pool of patients eligible for third line trastuzumab in the future. It was assumed that the quantity of trastuzumab used for third line treatment will not increase beyond the current trends. However, DUSC considered that the extent of use of trastuzumab was uncertain and could potentially increase with the increase in the prevalent population.

Risk Sharing Arrangement and estimates



subsidisation caps for a financial risk sharing arrangement thereby sharing the risk of excessive expenditure with the Government.

This review examined the estimate of use and cost agreed by Roche and the Department and noted that the method used to apply these limits in the estimates may have resulted in a small overestimate of the caps in the risk sharing arrangement.

Previous DUSC reviews of medicines for the treatment of breast cancer

DUSC has not reviewed medicines listed for treatment of metastatic or locally advanced HER2 positive breast cancer.

Methods

PBS prescription data for all PBS item codes used to treat breast cancer were extracted from the Department of Human Services (DHS) prescription database for date of supply from January 2003 to the end of September 2017. PBS items were selected on the basis of having the words “breast cancer” in the restriction text for at least one of the indications for the item.

As per the request from DUSC, the main focus was on trastuzumab, T-DM1 and pertuzumab. Table A.1 in Appendix A shows the PBS items, restriction code and breast cancer stages for these medicines. The disease stage was derived from the restriction text associated with each restriction code.

Information in Table A.1 was used to allocate a cancer disease stage to a prescription. All items for trastuzumab, T-DM1 and pertuzumab are Authority Required and this means that the restriction code should be recorded in the DHS Authority Approvals database. All items for these medicines are for HER2 positive breast cancer, so it is only necessary to use the

restriction code to determine the stage of the cancer (i.e. Early, Locally advanced, Metastatic or “Grandfathered”). “Grandfathered” refers to patients who commenced treatment prior to subsidy commencing on the PBS but who would have been eligible to commence PBS treatment.

The prescription data was matched to the authority approval data based on the patient ID, PBS item code and the dates of supply and approval. After undertaking this process, there were some prescriptions that lacked a restriction code, either because the matched authority approval had no recorded restriction code or there was no matching authority approval found. To increase the percentage of prescriptions with an allocated disease stage, if the PBS item has only one stage (e.g. item 6497Y in Table A.1 is only for Early stage) then the stage allocation was made on the basis of the item code only, without regard to the authority approval restriction code.

For other PBS medicines indicated to treat breast cancer the allocation of restriction code and breast cancer stage was more complex. Some items are Authority Required (Streamlined) (see items with Restriction Type = S in Attachment 1) and for these items the restriction code is recorded in the DHS prescription database instead of the DHS Authority Approvals database. For these items the Streamlined restriction code was used to determine the restriction text and the stage of cancer (even if an alternative restriction code also existed in the DHS Authority Approvals database. This can occur if there are increased quantity or repeats requested for a Streamlined item). In addition flags were constructed to indicate if the restriction code and text was for breast cancer (i.e. some items are also indicated for other cancers) and to indicate if the restriction code and text was for HER2 positive cancer or not. Table 1 in Attachment 1 shows the PBS items, breast cancer flag, HER2 positive flag and breast cancer stages for these medicines.

As noted in the “Relevant aspects of consideration by the PBAC” section of this report, for pertuzumab a maximum of [REDACTED] cycles of treatment per patient ([REDACTED] months) was proposed by Roche and accepted by the PBAC [REDACTED]. For T-DM1, a maximum of [REDACTED] cycles per patient lifetime ([REDACTED] months) was proposed by Roche and accepted by the PBAC [REDACTED].

To test if the number of cycles was limited to [REDACTED] for pertuzumab and [REDACTED] for T-DM1 in practice, the distribution of number of prescriptions per patient (see “Duration of therapy” section) was calculated.

- For pertuzumab, the analysis cohort was those patients that initiated pertuzumab in the first six months of listing (i.e. July 2015 to the end of December 2015, n=546). All these patients were followed up for exactly 21 months from their individual initiation date (this was the maximum follow-up possible as the data were only complete to the end of September 2017). 21 months provided the opportunity for 31 scripts to be supplied assuming a standard 21 days cycle without breaks in therapy.
- For T-DM1, the analysis cohort was those patients that initiated pertuzumab in the first three months of listing (i.e. July 2015 to the end of September 2015, n=258). All these patients were followed up for exactly 24 months from their individual initiation date (this was the maximum follow up possible as the data were only complete to the end of

September 2017). 24 months provided the opportunity for 35 scripts to be supplied assuming a standard 21 days cycle without breaks in therapy.

The duration of treatment analysis used the Kaplan Meier (aka Product-Limit) method to determine the length of treatment for patients on pertuzumab and T-DM1. Two ways of measuring length of treatment were undertaken. One excluded any breaks in treatment and the other did not. A break in treatment was defined as a gap of more than 3 times the median time to resupply between supplies, which was an estimated break in treatment of at least 2 times the median time to resupply. A patient was deemed to be continuing treatment (classified as censored in the Product-Limit method) at the end of the data period (i.e. the end of September 2017) if their last prescription was within 3 times the median time to resupply of this end date. Otherwise the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply or the end of the data period, whichever was later.

Results

1. Utilisation analyses

Trastuzumab (in all stages of breast cancer)

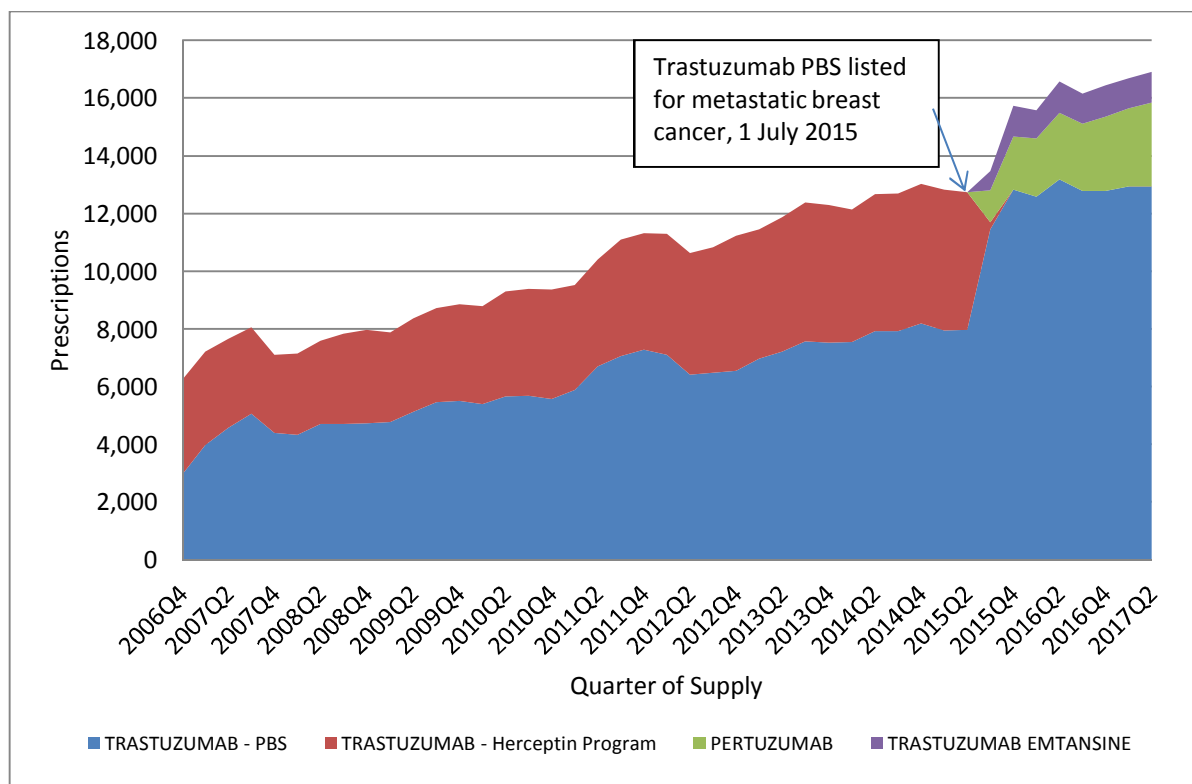


Figure 1: Prescriptions for trastuzumab, pertuzumab and trastuzumab emtansine (T-DM1) for the treatment of early stage, locally advanced and metastatic breast cancer. Source: DHS R/PBS prescription claims database (accessed 13/11/2017). Reports on Herceptin Program supplied by DHS.

The number of prescriptions of trastuzumab increased steadily from 2006 Q4, when it was PBS listed for early stage HER2 positive breast cancer (i.e. 1 October 2006) until 2015 Q2, when it was listed for metastatic HER2 positive breast cancer on 1 July 2015. Trastuzumab emtansine (T-DM1) and pertuzumab were also listed on this date. Utilisation of T-DM1 has remained steady since listing and pertuzumab has increased.

Prior to 1 July 2015 trastuzumab for metastatic breast cancer was supplied through another government program. To allow for incorporation supply of trastuzumab through the Herceptin Program and supply through the PBS, Figure 1 incorporates counts of 'patient orders'; these can be regarded as PBS prescriptions as the quantity supplied was essentially the same. The number of patient orders in 2015 Q3 (slightly less than 5,000) was consistent with the number of prescriptions per quarter for metastatic disease shortly after it was PBS-listed for this indication in July 2015.

Trastuzumab was also listed for locally advanced HER2 positive breast cancer on 1 December 2012 (see Figure 2), but this did not make a noticeable impact on the trend in Figure 1.

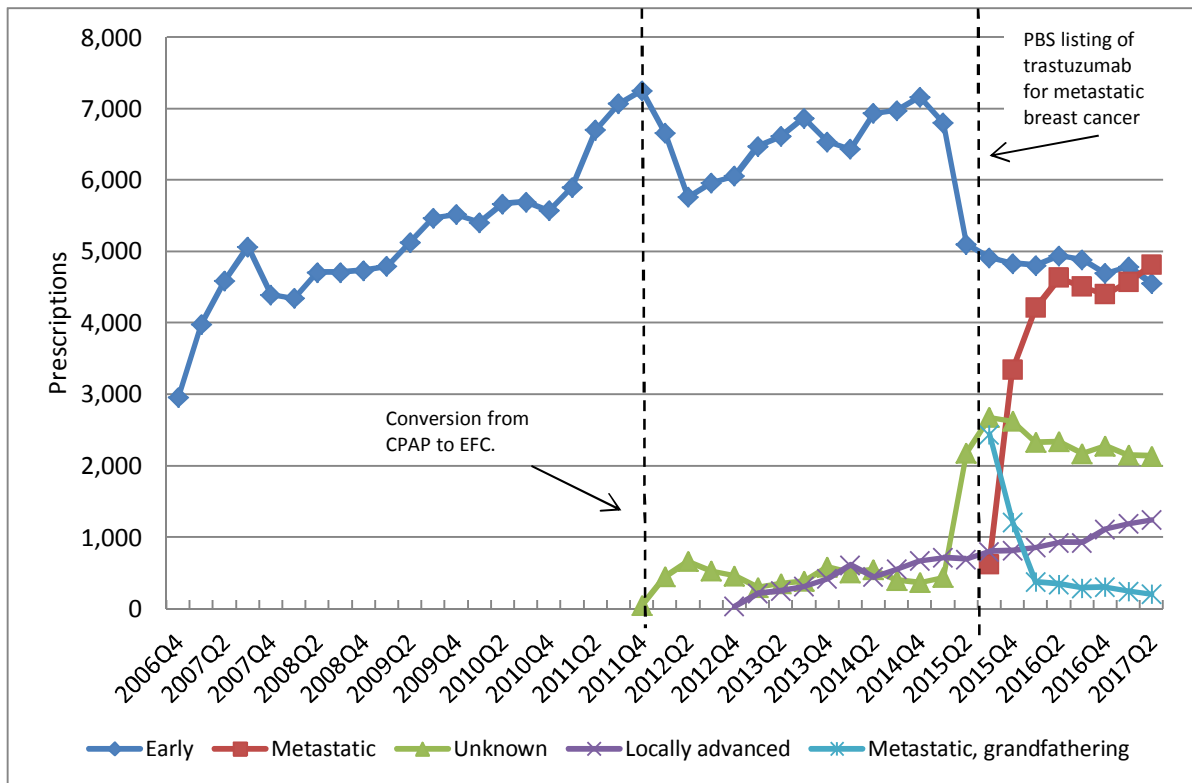


Figure 2: R/PBS Prescriptions for trastuzumab by disease stage.

Prescriptions for MBC prior to 1 July 2015 (ie. Herceptin Program data) are not included in this figure. Source: DHS R/PBS prescription claims database (accessed 13/11/2017)

Figure 2 shows an apparent large drop in the utilisation of trastuzumab for early breast cancer in 2015 Q2, which is the quarter before the listing of trastuzumab for metastatic disease on 1 July 2015. The increase in “Unknown” disease stage is approximately equal to the decrease in early stage disease. Upon investigation it appears that this was due to utilisation changing from the item code 7267L (Powder for I.V. infusion 100 mg, S100 EFC, Private Hospital, Continuing treatment) to 4703M (Powder for I.V. infusion 100 mg, S100 EFC, Public Hospital, Continuing treatment). The problem was that although the restriction code data was recorded in the Private Hospital setting, this was not the case in the Public Hospital setting, leading to an increase in “Unknown” disease stage prescriptions. Both these item codes have indications for Early and Locally advanced, however the Locally advanced time series does not appear to be affected by this problem. Thus to simplify the figures, this review combined the Early and Unknown indications and the Metastatic and Metastatic- grandfathered (See Figure 3).

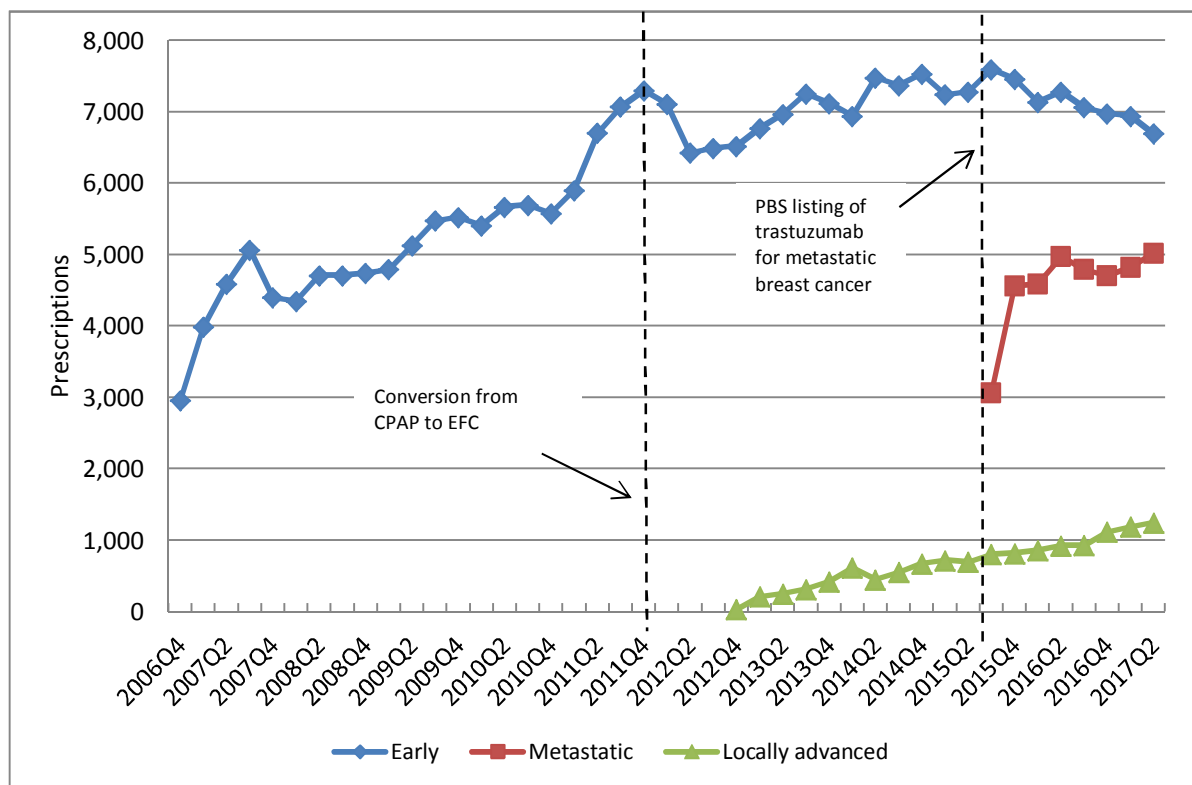


Figure 3: R/PBS Prescriptions for trastuzumab by disease stage consolidated to include grandfathered in the metastatic group and unknown in the early stage group (refer to text).

Prescriptions for MBC prior to 1 July 2015 (ie. Herceptin Program data) are not included in this figure. Source: DHS R/PBS prescription claims database (accessed 13/11/2017)

Figure 3 shows that the prescription utilisation of trastuzumab for early disease started to decline after it was listed for metastatic disease. This may indicate that there was some use outside of restriction prior to the listing for metastatic disease.

The time series of trastuzumab for early breast cancer in Figure 3 shows that the number of prescriptions before and after the start of the Efficient Funding of Chemotherapy Drugs initiative (EFC) (2011 Q4) was quite consistent and so, in this case, the prescriptions prior to EFC seem to correspond to a single infusion. Revised prescribing and dispensing arrangements for certain chemotherapy drugs subsidised by the PBS came into effect on 1 December 2011 under the Revised Arrangements for the EFC. Prior to this the medicines were available via the Section 100 Chemotherapy Pharmaceutical Access Program (CPAP) special arrangements for Public Hospital prescribing and via PBS section 85 general schedule for Private Hospital prescribing. The transition from CPAP to EFC changed the definition of a prescription. Under CPAP a prescription specified a number of vials of medicine for infusion which may have been sufficient for one or multiple infusions. Under EFC a prescription specifies a single infusion only and also specifies the patient’s dose and number and size of vials paid for by the government.

Two components of trastuzumab utilisation data are not represented in Figure 3. The main component comes from the non-PBS Herceptin Program, which began in December 2001 and ceased at the end of July 2015; a month after trastuzumab for metastatic breast cancer was listed on the PBS. Utilisation for this program is shown in Figure 4 and incorporated into Figure 1.

A minor second component that is missing from Figure 3 is the PBS trastuzumab utilisation data that was processed via the HSD bulk processing for public hospitals prior to the introduction of EFC. Not all prescriptions from public hospitals were available at the patient level prior to transition to EFC (December 2011). This is because some of the utilisation was processed via a bulk processing system. This has a small impact on the prescription volume in Figure 3. It was estimated from the DUSC HSD database (which contains all utilisation, including from the bulk processing system) that only 3% of utilisation prior to 2012 Q1 is missing from Figure 3.

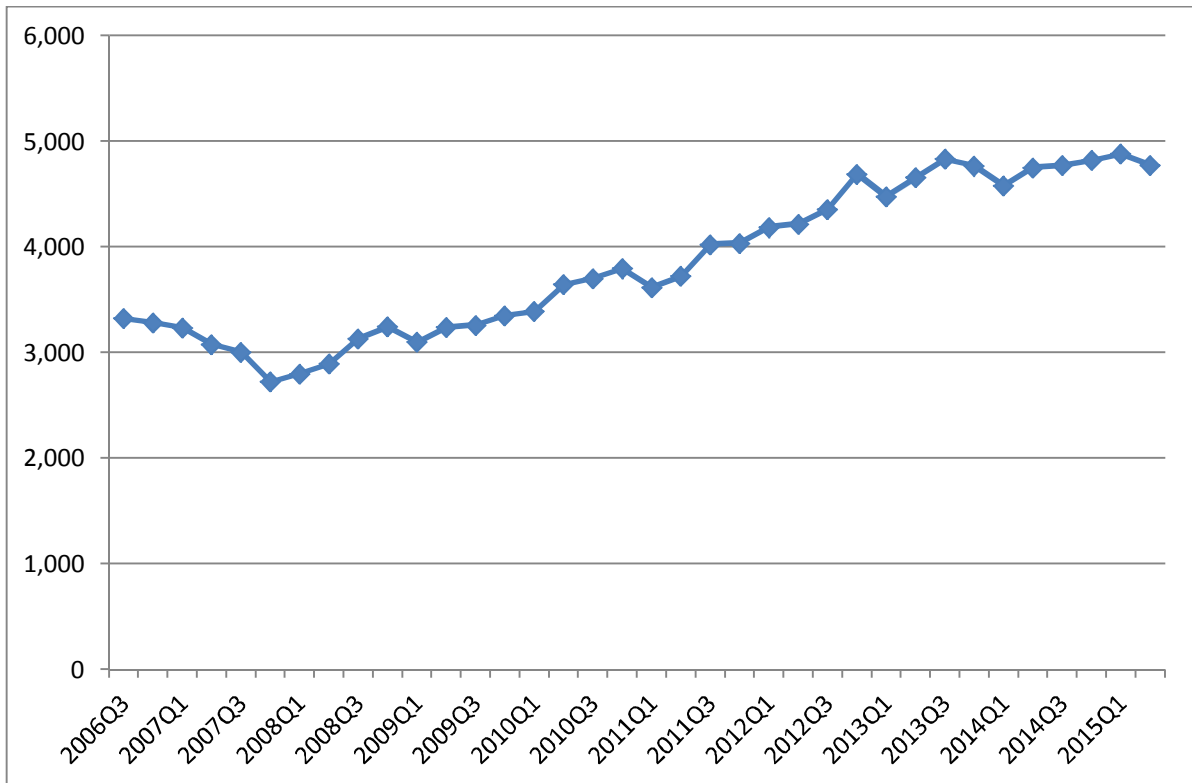


Figure 4: Number of patient orders by Herceptin program

Source: DHS Complex Drugs (Tasmania) reports on Herceptin program supplied by DHS (final report received in November 2015)

Trastuzumab emtansine (T-DM1)

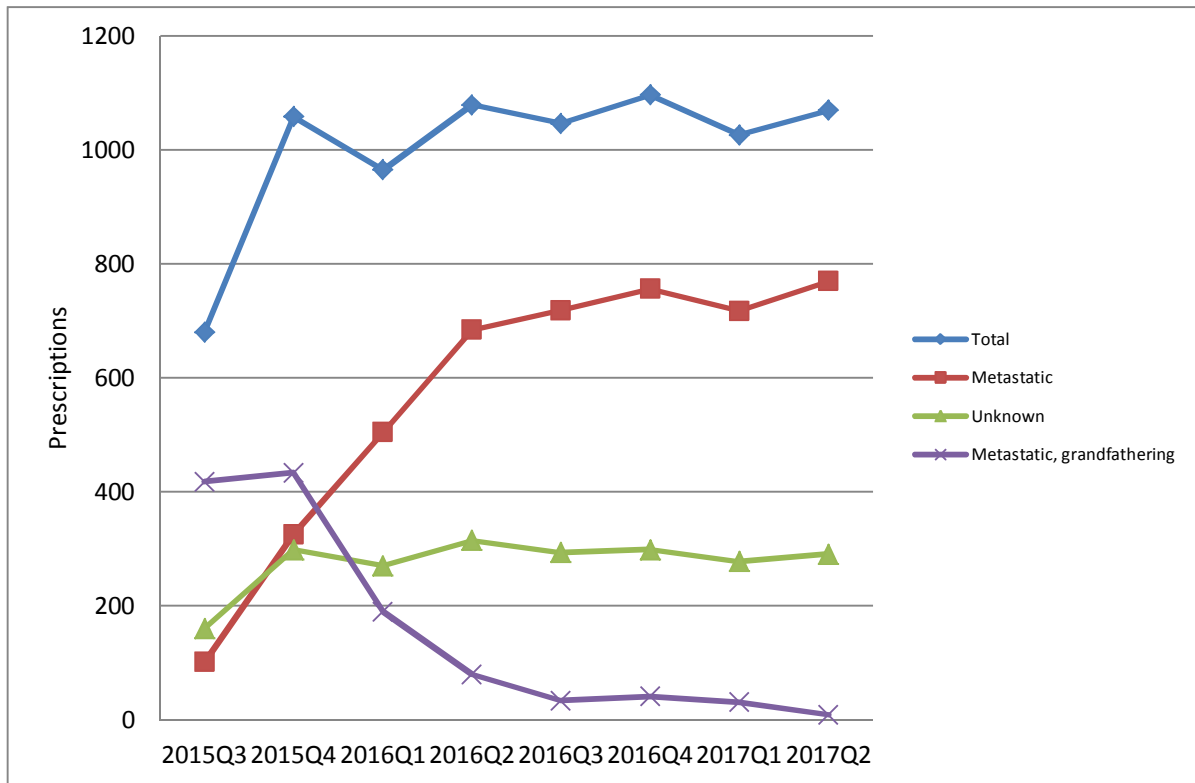


Figure 5: R/PBS Prescriptions for T-DM1 by disease stage

Source: DHS R/PBS prescription claims database (accessed 13/11/2017)

T-DM1 is PBS subsidised for metastatic breast cancer (PBS items 10281D, 10282E). The PBAC agreed that patients who were on treatment prior to PBS listing should continue to access T-DM1 and these patients are designated as “grandfathered” with a separate restriction code for grandfathered and those initiating therapy. The same issues outlined above with respect to “unknown” restriction codes apply here and while the “unknown” category is still for metastatic disease it is not known if the patient was “grandfathered” or not. Nearly all the instances of “unknown” come for the public hospital specific item 10282E. This item requires a written authority application and so there seems to be a system problem with the recording of restrictions in the DHS authority approvals database from public hospital applications.

Pertuzumab

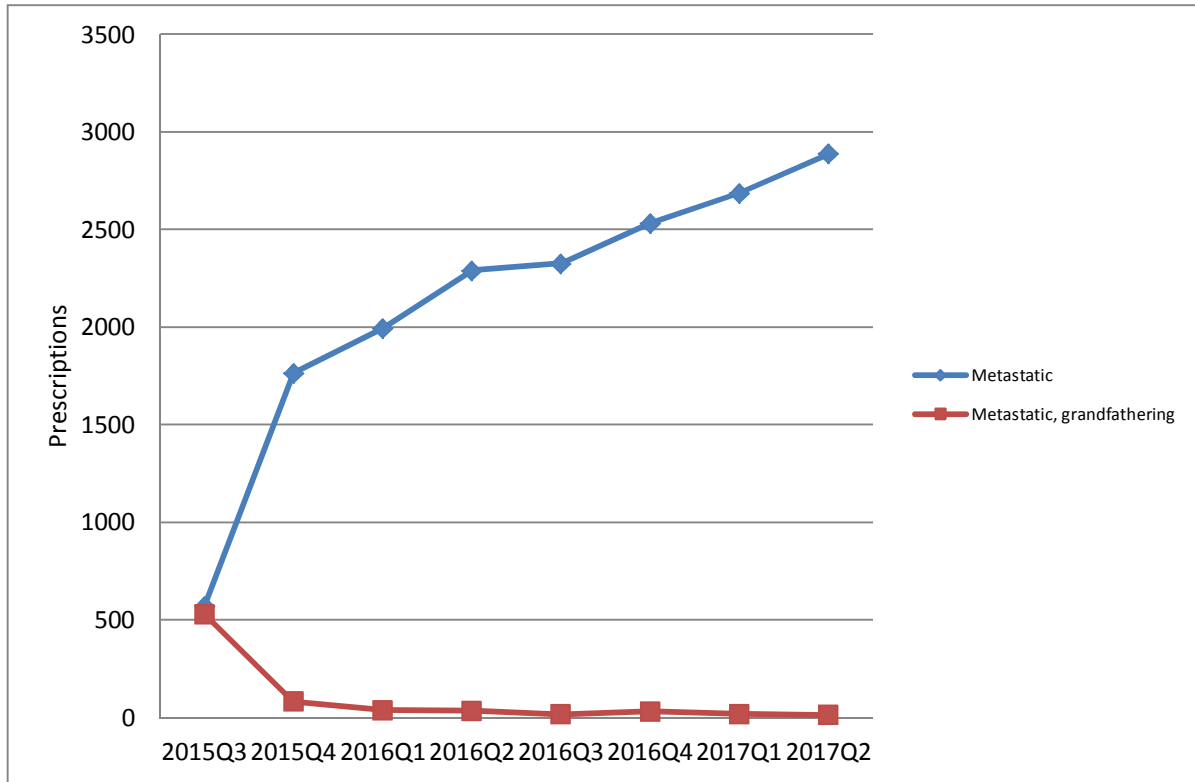


Figure 6: R/PBS Prescriptions for pertuzumab by disease stage

Source: DHS R/PBS prescription claims database (accessed 13/11/2017)

Pertuzumab is PBS subsidised for metastatic disease (PBS items - 10267J, 10268K, 10308M, 10309N, 10333W, 10334X). These item codes are indication specific to “Metastatic” or “Metastatic grandfathering”, so there was no need to rely on the authority approval restriction code to allocate indication to prescriptions. Thus there is no “Unknown” disease stage in Figure 6.

Utilisation of all PBS and RPBS subsidised medicines for HER2 positive breast cancer.

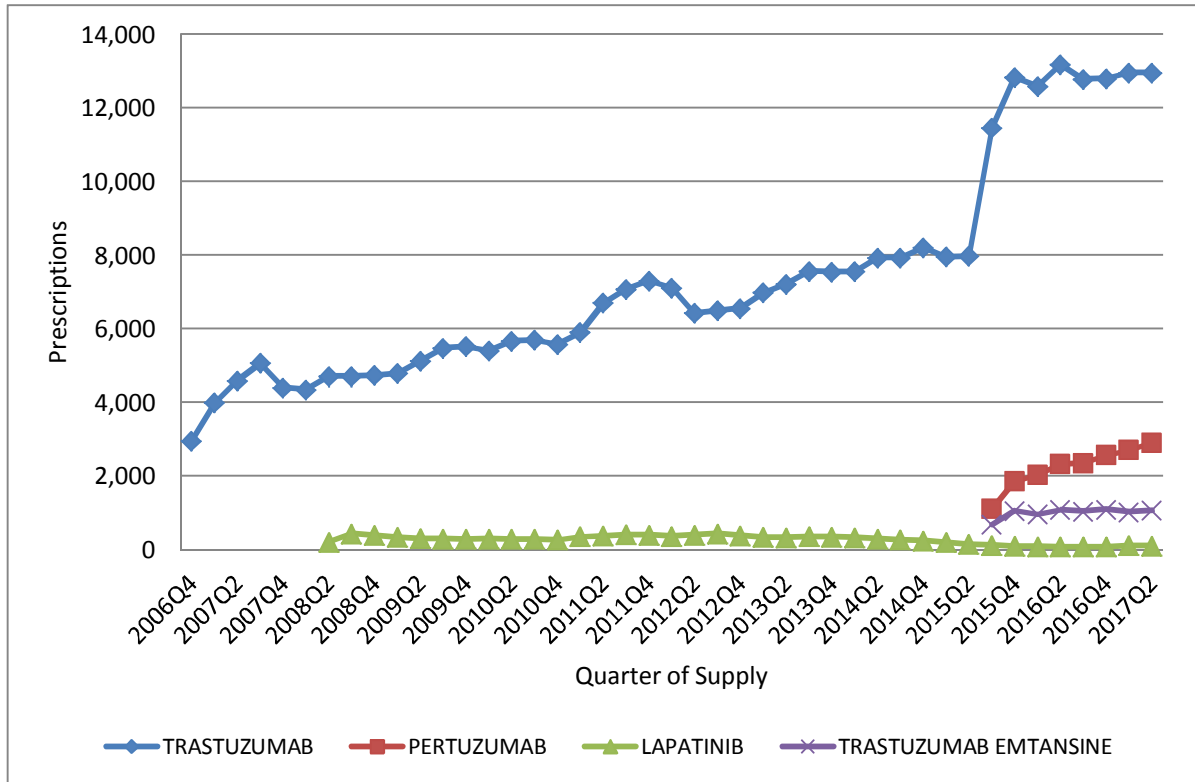


Figure 7: R/PBS Prescriptions for PBS subsidised HER2 inhibitors for early, locally advanced and metastatic HER2 positive breast cancer. Trastuzumab prescriptions for MBC prior to 1 July 2015 (ie. Herceptin Program data) are not included in this figure. Source: DHS R/PBS prescription claims database (accessed 13/11/2017)

Lapatinib has been listed for metastatic breast cancer since 1 May 2008. Use of lapatinib has been quite low.

Initiating and prevalent patient counts

This section reports the numbers of patients who commence treatment (initiating) and who are on treatment (prevalent) in each quarter. As patients may continue from one quarter to the next the prevalent counts per quarter cannot be added together to report the yearly prevalence.

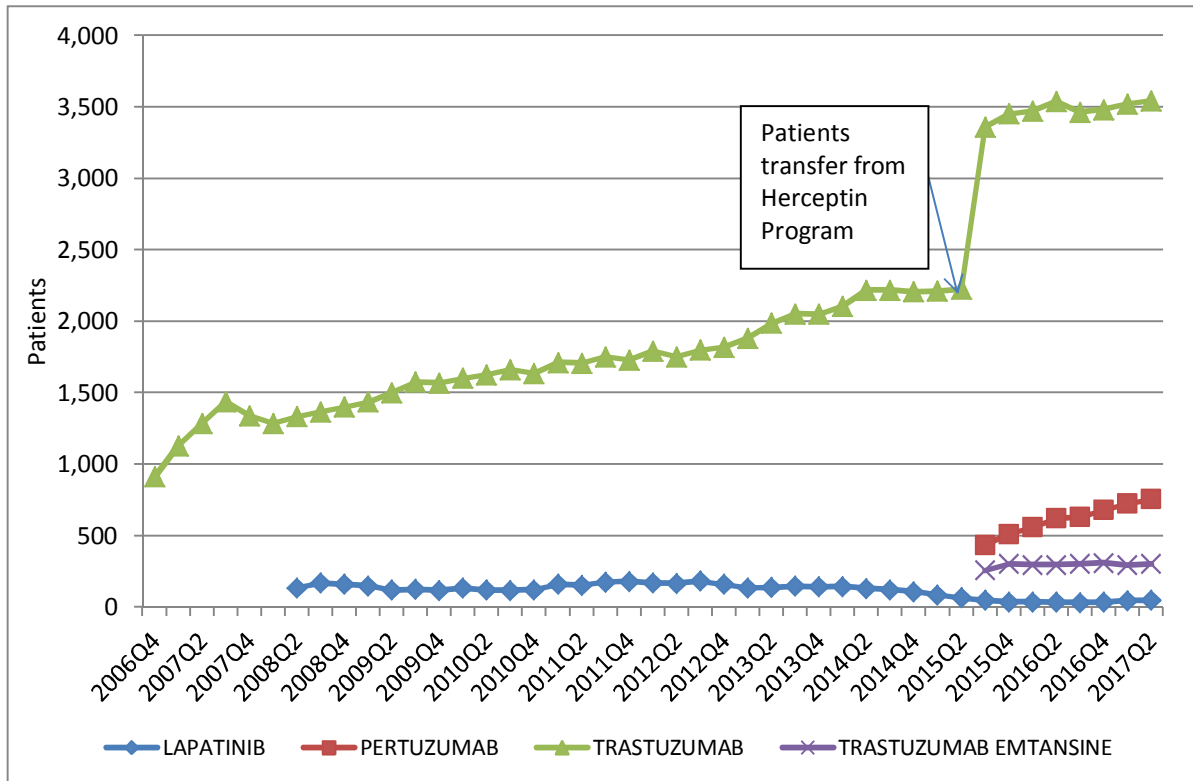


Figure 8: Prevalent patients per quarter by PBS listed medicine.

Trastuzumab prescriptions for MBC prior to 1 July 2015 (ie. Herceptin Program data) were not used in this figure. Source: DHS R/PBS prescription claims database (accessed 13/11/2017).

Figure 9 shows the medicines in Figure 8 broken down by stage of disease.

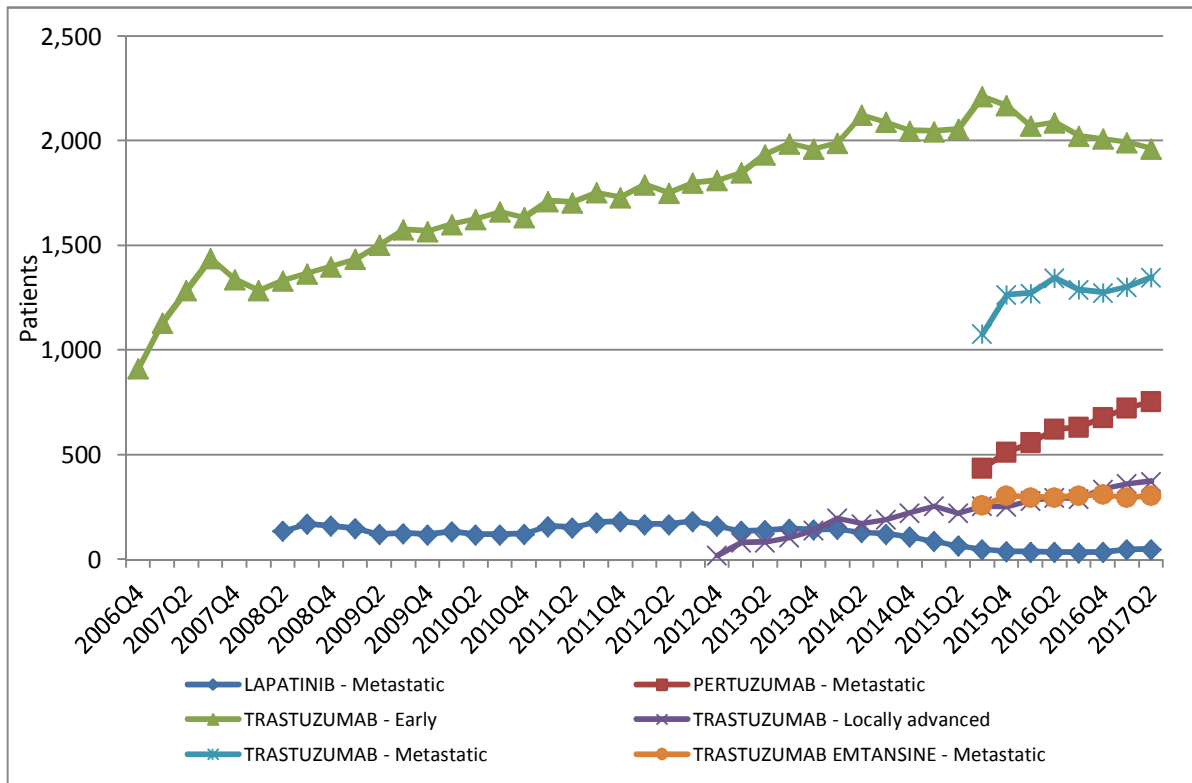


Figure 9: Prevalent patients per quarter by PBS listed medicine and stage of disease

Trastuzumab prescriptions for MBC prior to 1 July 2015 (ie. Herceptin Program data) were not used in this figure. Source: DHS R/PBS prescription claims database (accessed 13/11/2017)

The reduction in number of prescriptions dispensed for trastuzumab following PBS listing of pertuzumab and T-DM1 was identified in Figure 3 and is reflected in lower numbers of patients being treated for early breast cancer by trastuzumab in Figure 9. This supports the view that some patients receiving early breast cancer treatment may have had metastatic disease or have progressed while on treatment for early breast cancer and only switched when trastuzumab for MBC was listed.

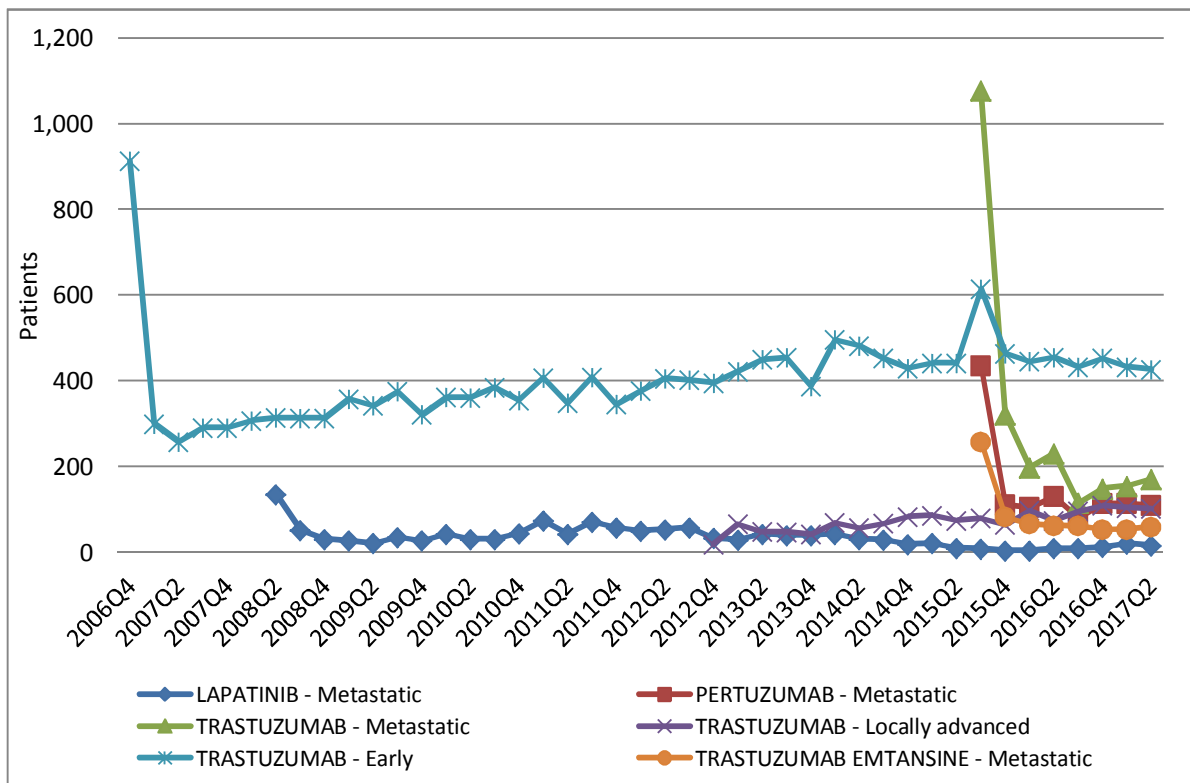


Figure 10: Number of patients initiating PBS listed medicines for the treatment of HER2 positive breast cancer by stage of disease. Trastuzumab prescriptions for MBC prior to 1 July 2015 (ie. Herceptin Program data) were not used in this figure. Source: DHS R/PBS prescription claims database (accessed 13/11/2017)

Patients initiating PBS therapy with trastuzumab includes patients transferring from the non-PBS Herceptin Program. A proportion of patients initiating pertuzumab and T-DM1 will have been treated by non-PBS supplied medicine prior to listing (aka grandfathered patients).

Figure 10 shows that from quarter 3 2016 (after grandfathering patients have commenced PBS-listed medicine) approximately 150 patients per quarter are commencing treatment with trastuzumab, around 100 are commencing pertuzumab (presumably with trastuzumab) and around 60 are commencing T-DM1.

Therefore around 50 patients are initiating trastuzumab as monotherapy or with other agents.

2. Analysis of predicted versus actual utilisation

This analysis compares the predicted and actual use of use of trastuzumab, T-DM1 and pertuzumab for MBC. The predicted use was extracted from final agreed estimates between Roche and the Department of Health. The PBS items and restriction codes included in this analysis of actual utilisation are specified in Appendix A.

Table 3: Predicted vs Actual analysis – trastuzumab for MBC

		Year1	Year 2
		July 15 to June 16	July 16 to June 17
Treated Prevalent patients (PBS & RPBS)	Predicted (P)	■	■
	Actual (A)	1,828	1,834
	% Difference (A-P)/P	■	■
Prescriptions	Predicted (P)	■	■
	Actual (A)	17,191	19,337
	% Difference (A-P)/P	■	■
Prescriptions per patient	Predicted (P)	■	■
	Actual (A)	9.4	10.5
	% Difference (A-P)/P	■	■
R/PBS expenditure (published)	Predicted (P)	■	■
	Actual (A)	\$54,263,546	\$59,040,768
	% Difference (A-P)/P	■	■

Source: Predicted values - Final agreed estimates; actual values - DHS R/PBS prescription claims database (accessed 13/11/2017)

The actuals in Table 3 include trastuzumab for MBC used in combination with pertuzumab as well as for second and subsequent lines.

The calculations to determine the expected use of trastuzumab incorporated use in first-line patients in combination with pertuzumab (assumed to 95% of all incident patients with metastatic breast cancer), the remaining use as monotherapy (5%), and use in third line in patients whose disease has worsened while on second-line treatment with either lapatinib or T-DM1 or who were receiving trastuzumab monotherapy while on the Herceptin Program.

Total number of patients and the number of prescriptions supplied was more than predicted. The number of prescriptions per patient was less than predicted: in part this can be attributed to the method of calculation of pertuzumab prescriptions in the predicted estimates (ie. not adequately allowing for patients to commence treatment throughout the year) and the corresponding trastuzumab prescriptions, and some to the slower uptake of T-DM1 resulting in greater use of trastuzumab. In addition this method of calculating the number of prescriptions per patient does not adjust for time on treatment. Further analysis of duration of treatment is provided later in this report.

Table 4: Predicted vs Actual analysis - T-DM1 for MBC

		Year1	Year 2
		July 15 to June 16	July 16 to June 17
Treated Prevalent patients (PBS & RPBS)	Predicted (P)	■	■
	Actual (A)	468	475
	% Difference (A-P)/P	■	■
Prescriptions	Predicted (P)	■	■
	Actual (A)	3,786	4,237
	% Difference (A-P)/P	■	■
Prescriptions per patient	Predicted (P)	■	■
	Actual (A)	8.1	8.9
	% Difference (A-P)/P	■	■
R/PBS expenditure (published)	Predicted (P)	■	■
	Actual (A)	\$16,615,379	\$18,605,819
	% Difference (A-P)/P	■	■

Source: Predicted values - Final agreed estimates; actual values - DHS R/PBS prescription claims database (accessed 13/11/2017)

For T-DM1, the number of treated patients, prescriptions, and prescriptions per patient were all lower than predicted. The patient numbers may reflect slower uptake of this treatment. Possible contributing factors include patients not commencing second line therapy as quickly as expected in the model, fewer patients being considered suitable for therapy and more being maintained on trastuzumab monotherapy as second line or other chemotherapy as third or fourth line.

Table 5: Predicted vs Actual analysis – pertuzumab for MBC

		Year1	Year 2
		July 15 to June 16	July 16 to June 17
Treated Prevalent patients (PBS & RPBS)	Predicted (P)	■	■
	Actual (A)	781	976
	% Difference (A-P)/P	■	■
Prescriptions	Predicted (P)	■	■
	Actual (A)	7,303	10,509
	% Difference (A-P)/P	■	■
Prescriptions per patient	Predicted (P)	■	■
	Actual (A)	9.4	10.8
	% Difference (A-P)/P	■	■
R/PBS expenditure (published)	Predicted (P)	■	■
	Actual (A)	\$25,062,327	\$35,003,142
	% Difference (A-P)/P	■	■

Source: Predicted values - Final agreed estimates; actual values - DHS R/PBS prescription claims database (accessed 13/11/2017)

Prescription utilisation of pertuzumab was less than predicted in Year 1 and more than predicted in Year 2. Across the two years prescription utilisation was approximately equal to predicted. The number of patients was greater than predicted. DUSC considered that uptake

of pertuzumab would be around 100%, although 95% was used in the model. The number of prescriptions per patient was less than predicted in both years. This review identified that the model did not adequately account for patients commencing treatment throughout the year and so the predicted prescriptions per patient and associated costs were a small overestimate. Refer to Section 3 for further information on duration of treatment analysis.

Table 6: Combined prescriptions and R/PBS expenditure for trastuzumab, T-DM1 and pertuzumab for MBC.

		Year1	Year 2
		July 15 to June 16	July 16 to June 17
Prescriptions	Predicted (P)	██████	██████
	Actual (A)	28,280	34,083
	% Difference (A-P)/P	██	██
R/PBS expenditure (published)	Predicted (P)	██████████	██████████
	Actual (A)	\$95,941,252	\$112,649,729
	% Difference (A-P)/P	██	██

Source: Predicted values - Final agreed estimates; actual values - DHS R/PBS prescription claims database (accessed 13/11/2017)

The combined prescription utilisation for the three drugs was ██████% more than predicted in Year 1. This increased in Year 2 to ██████% more than predicted. The more than predicted utilisation of trastuzumab is cancelled out to some extent by the less than predicted use of T-DM1.

The estimates were based on the number of patients treated for metastatic disease on the Herceptin Program using the average increase per annum to impute future patient numbers. As patients are expected to remain on treatment for longer periods of time with the new pharmacotherapies available, the prevalence of treated patients will increase, so the model may have underestimated the increase in prevalence.

3. Duration of therapy

Prescriptions per patient

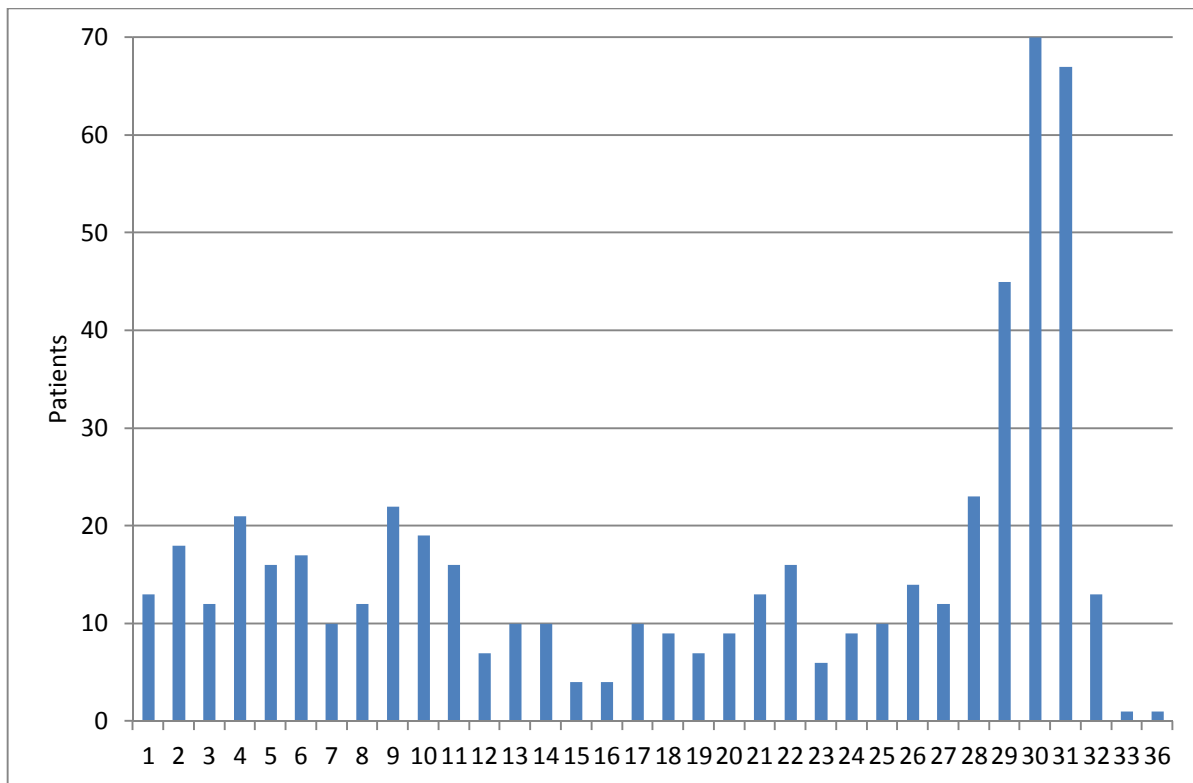


Figure 11: Distribution of the number of pertuzumab prescriptions per patient in the 21 months post initiation. Source: DHS R/PBS prescription claims database (accessed 30/11/2017)

As per the Method section, the number of patients in this analysis was 546 (i.e. initiators from July 2015 to the end of December 2015). It can be seen from Figure 11 that a number of patients received more than [REDACTED] prescriptions. [REDACTED] Patients with around 31 prescriptions in the data were regarded as continuers throughout the whole 21 months period using a 21 day cycle (i.e. a patient receiving the original and then a supply every 21 days for 21 months would receive 31 prescriptions). There are 197 (26.1%) patients who were supplied 29 or more prescriptions in the 21 months post initiation. These patients are most likely continuing treatment.

It is not possible from this analysis to determine if this reflects a difference in how pertuzumab is being prescribed in Australian clinical practice compared to the clinical trial. If the longer term use is in patients who have disease progression then this use may not be consistent with the model parameters and inputs that underpinned the PBAC's decision that pertuzumab was cost-effective. *Further analysis of the utilisation pattern of pertuzumab may be warranted.*

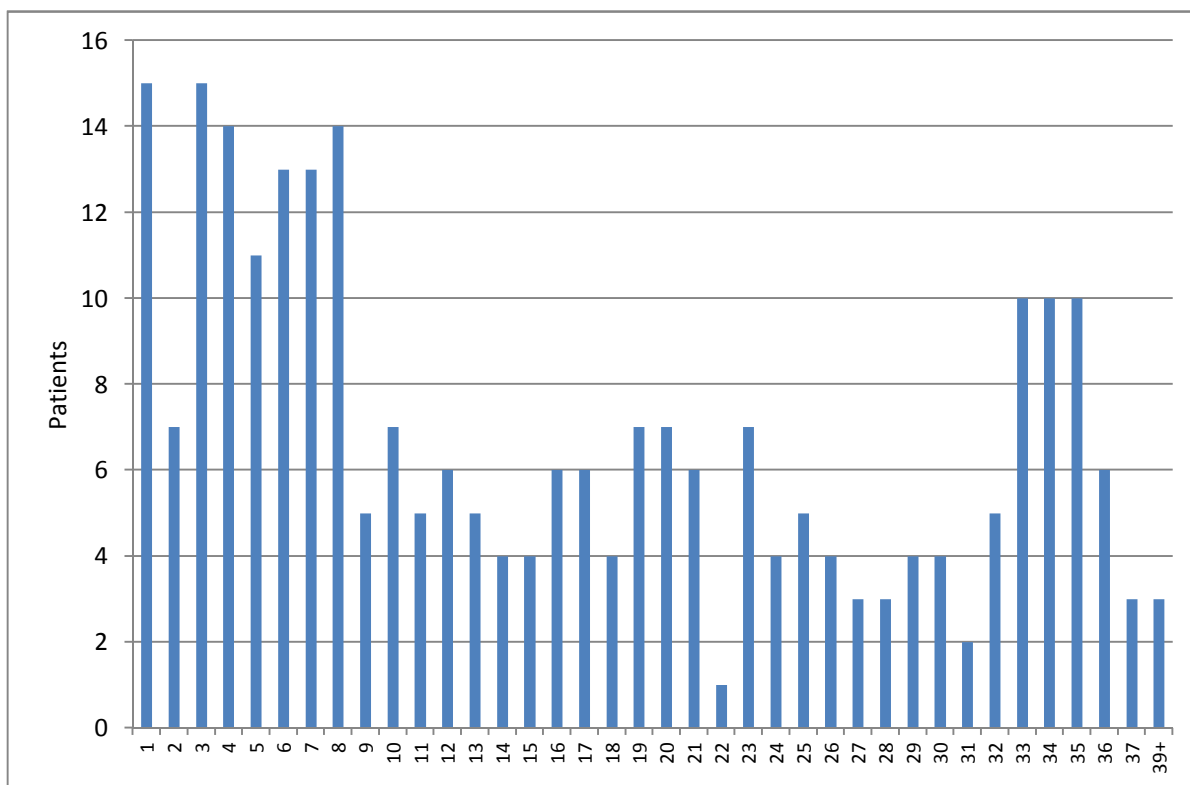


Figure 12: Distribution of the number of T-DM1 prescriptions per patient in the 24 months post initiation. Source: DHS R/PBS prescription claims database (accessed 30/11/2017)

As per the Method section, the number of patients in this analysis is 258 (i.e. initiators from July 2015 to the end of September 2015).

Patients with around 35 prescriptions in the data should be interpreted as continuers throughout the whole 24 month period using a 21 day cycle (i.e. a patient receiving the original and then a supply every 21 days for 24 months would receive 35 prescriptions).

The pattern of supply for T-DM1 is different to that for pertuzumab. A substantial proportion of patients commencing T-DM1 have 8 or less cycles. Further investigation into this trend in the future may be warranted.

Time to resupply and length of treatment

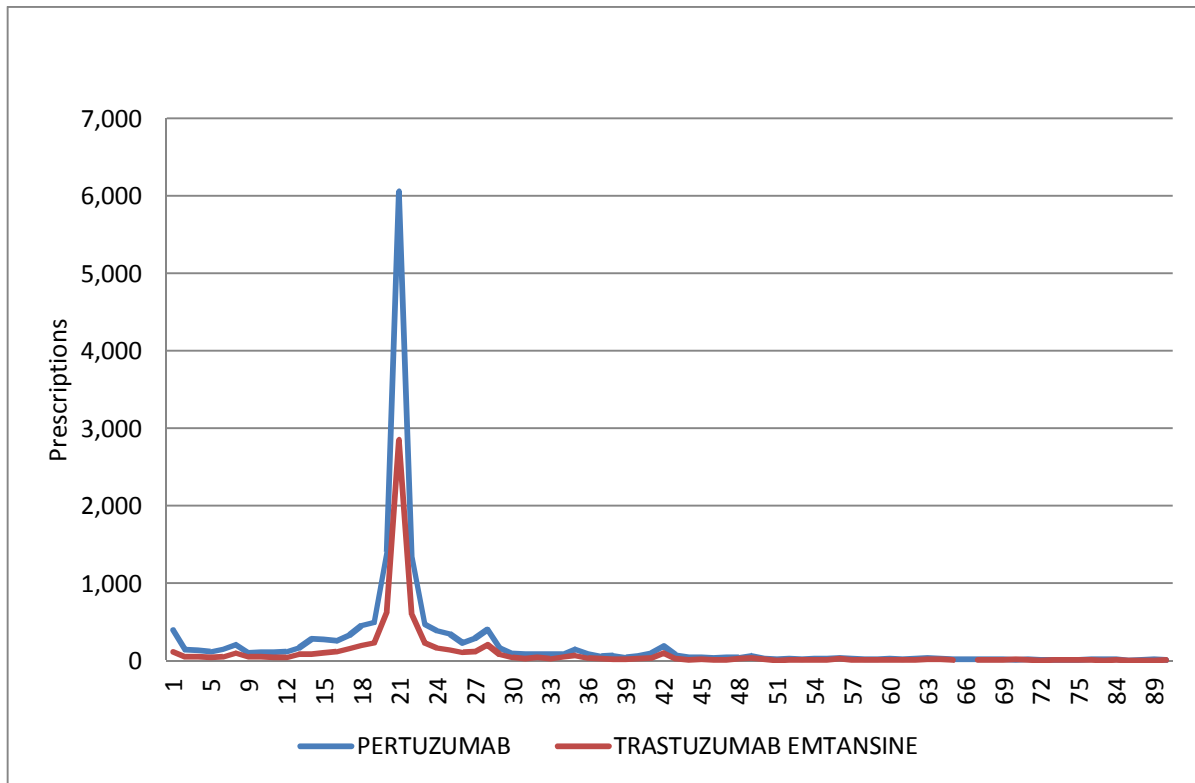


Figure 13: Number of days to prescription resupply by drug

Note: does not include prescriptions with no resupply and resupply > 90days

Source: DHS R/PBS prescription claims database (accessed 30/11/2017)

Figure 13 shows that the most common (mode) time to resupply for both drugs was 21 days. There were also minor peaks at 28, 35 and 42 days. The median time to resupply for both drugs was 21 days. This was used in the following length of treatment analysis to determine breaks in treatment (see Methods for details).

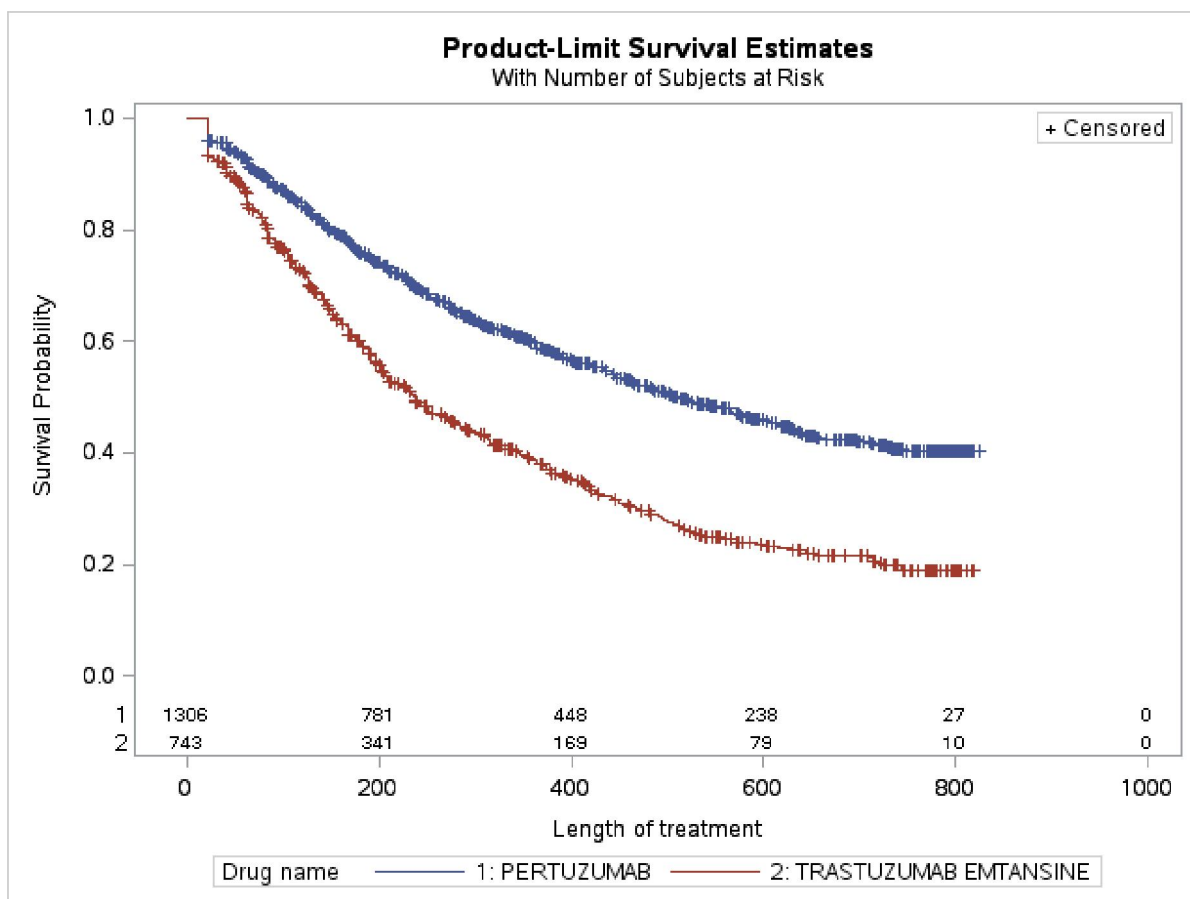


Figure 14: Length of treatment (excluding breaks) by drug

Source: DHS R/PBS prescription claims database (accessed 30/11/2017)

The median length of treatment (excluding breaks) on pertuzumab and T-DM1 was 508 days (16.7 months) and 237 days (7.8 months) respectively. The length of treatment (including breaks) was also calculated (Figure 15). The median length of treatment (including breaks) on pertuzumab and T-DM1 was 532 days (17.5 months) and 265 days (8.7 months) respectively. The differences between the medians of the two types of length of treatment (including and excluding breaks) were 24 days and 28 days for pertuzumab and T-DM1 respectively.

█ cycles of pertuzumab treatment was estimated in the submission to take █ months assuming continuous treatment. This is slightly shorter than the actual median 16.7 months' worth of treatment (excluding breaks) measured in this analysis. However this analysis is affected by the short observation time.

█ cycles of T-DM1 treatment was estimated in the submission to take █ months assuming continuous treatment. This is longer than the actual median 7.8 months' worth of treatment (excluding breaks) measured in this analysis. This could reflect the clinical characteristics of patients receiving second line treatment or issues of tolerance and toxicity associated with T-DM1. It may also reflect use of T-DM1 as a last resort after multiple lines of treatment with pertuzumab.

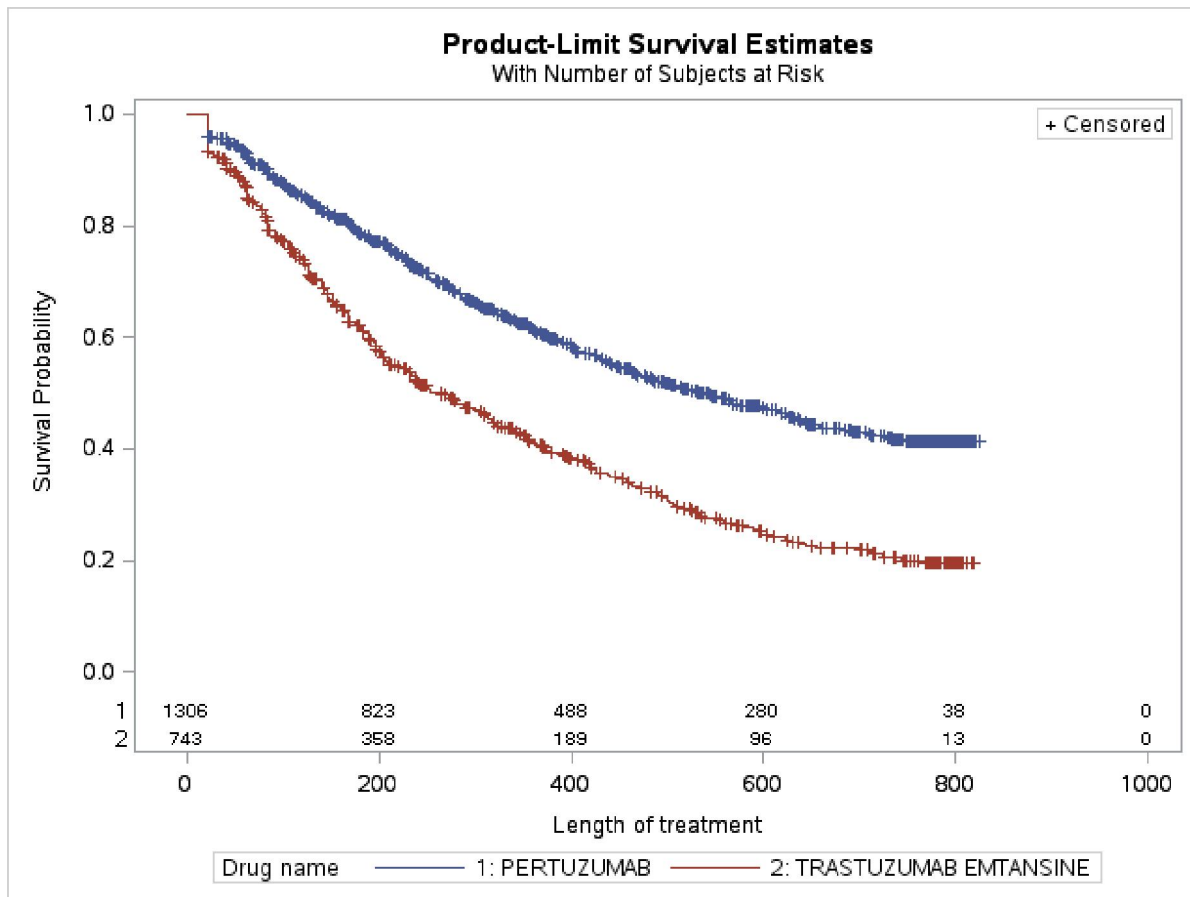


Figure 15: Length of treatment (including breaks) by drug

Source: DHS R/PBS prescription claims database (accessed 30/11/2017)

DUSC consideration

Pertuzumab is PBS subsidised for the treatment of HER2 positive metastatic breast cancer in combination with trastuzumab and a taxane in the first-line setting. Lapatinib and T-DM1 are PBS listed for treatment in patients who have progressive disease following first line therapy for metastatic disease. Trastuzumab was previously available through the Herceptin Program and since 1 July 2015 has been PBS subsidised for use in any line of therapy for metastatic HER2 positive breast cancer. The PBAC (November 2014) had considered that the restriction for trastuzumab should reflect current evidence and legitimise clinical practice by allowing use of trastuzumab beyond progression and with a range of partner chemotherapy options, with the exception of nab-paclitaxel. DUSC noted that the PBS restrictions for trastuzumab allow for a broad range of co-administered chemotherapy and use as monotherapy in some patients. DUSC also discussed the differing views of clinicians regarding what is a line of therapy. Clinicians may not consider a change in chemotherapy partner, while maintaining treatment with trastuzumab, to be a change in line of treatment.

The analysis (Figure 10) showed that from the third quarter of 2016 approximately 150 patients each quarter have a first PBS dispensing of trastuzumab for metastatic disease and

about 100 patients have a first dispensing of pertuzumab. DUSC noted that the use of trastuzumab is substantially more than pertuzumab. This difference occurred even though pertuzumab is partnered with trastuzumab in the first line treatment setting. While some use of trastuzumab without pertuzumab is expected in patients transitioning from the Herceptin Program, for later lines of therapy or patients with metastatic disease remaining classified in the data as having early breast cancer, there is a group of metastatic breast cancer patients who may not be commencing trastuzumab in combination with pertuzumab. Given the clinical trial results showed significant and important improvements with pertuzumab it is not clear why this would be the case. This is a potential quality use of medicines issue.

DUSC considered that the pertuzumab and T-DM1 utilisation data are still immature. Given the relatively small sample of patients who have sufficient time on therapy for a meaningful interpretation of the utilisation data, DUSC did not consider it was possible to confidently assess whether patients are transitioning to other therapies as their disease progresses. The analyses provided in the report showed that █% of patients receiving pertuzumab exceeded █ cycles and █% of patients on T-DM1 exceeded █ cycles. The Sponsor provided additional information from the TABITHA registry to support their view that patients are not continuing on pertuzumab plus trastuzumab longer than expected. However DUSC noted that the sample size of the TABITHA data was small and the representativeness of the data was unclear. DUSC agreed with the Sponsor that insight into the utilisation of both medicines is immature and treatment regimens are developing. In addition DUSC noted that cohort studies of trastuzumab treated patients in Australia show increasing survival time, longer time on therapy than predicted from clinical trials and preferences for switching chemotherapy partners while remaining on trastuzumab rather than commencing a second line of treatment⁶. DUSC also noted that the PBAC had not seen evidence of effectiveness of trastuzumab in a population treated with adjuvant trastuzumab for early breast cancer and subsequently trastuzumab in metastatic breast cancer. An Australian cohort study has shown that 20% of women treated for metastatic disease also had adjuvant treatment with trastuzumab.⁷

DUSC noted the actual prevalent trastuzumab treated population in each of the two years was reported to be almost triple that expected. DUSC noted that the trastuzumab utilisation data presented includes trastuzumab used in combination with pertuzumab as well as monotherapy or second and subsequent lines of therapy. DUSC considered that a statement should be added into the report to highlight this. The committee noted that the prevalence estimate was based on the Australian Government Herceptin Program which was considered the most reliable source for counting treated patients. There were some differences between the Herceptin Program and the PBS listing which may account to some extent for a difference in the treated population; in particular the requirement for a scan to demonstrate metastatic disease in the earlier Herceptin Program. Another reason for the underestimate of metastatic prevalent patients was that some may have been treated on the PBS under the early breast

⁶ Daniels et al Trastuzumab for metastatic breast cancer. Real world outcomes from an Australian whole-of-population cohort (2001-2016) *Breast* 2017; 38:7-13 doi: 10.1016/j.breast.2017.11.007

⁷ Daniels et al. Survival outcomes for Australian women receiving trastuzumab for HER2-positive metastatic breast cancer following (neo)adjuvant trastuzumab: a national population-based observational study (2006-2014) *British Journal of Cancer* 2017 doi: 10.1038/bjc.2017.405

cancer indication and so were not part of the Herceptin Program. These patients may have transitioned to PBS supply after trastuzumab was listed for this indication. There was a decline in the early breast cancer utilisation after July 2015 (Figure 9).

The prevalent treated population for pertuzumab was slightly higher than predicted, while T-DM1 was slightly less. DUSC advised the PBAC that 100% of eligible patients commencing pertuzumab was a possibility and the committee noted that the final estimate agreed between the Sponsor and the government was 95%: even considering higher uptake the prevalent population was possibly slightly underestimated for pertuzumab.

For the purposes of ensuring cost effective use, the expected financial expenditure was capped

[REDACTED]. The Sponsor further stated that the purpose of the risk sharing arrangement is to share financial risk and provide budget certainty. [REDACTED]

DUSC actions

- Further review by DUSC of trastuzumab, pertuzumab and T-DM1 in another 24 months when more data are available. The analyses should also examine the data for any trend in patients continuing to receive trastuzumab monotherapy in early lines of pharmacotherapy for metastatic disease.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Roche Products Pty Ltd (trastuzumab, pertuzumab and trastuzumab emtansine): The sponsor has no comment

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

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Appendix A: PBS Schedule information (as at 1 October 2017)

Table A.1: PBS items, restriction code and breast cancer stages for trastuzumab, trastuzumab emtansine and pertuzumab.

Drug Name	Item Code	Form and Strength	Stage	Restriction Code	Start Date (yyyymmdd)	End Date (yyyymmdd)
TRASTUZUMAB	04632T	Powder for I.V. infusion 60 mg	Early	3927	20111201	20121231
				4164	20121201	99990909
			Locally advanced	4142	20121201	99990909
	04639E	Powder for I.V. infusion 60 mg	Early	3929	20111201	20121231
				4156	20121201	99990909
			Locally advanced	4104	20121201	99990909
	04650R	Powder for I.V. infusion 60 mg	Early	3926	20111201	20121231
				4144	20121201	99990909
			Locally advanced	4143	20121201	99990909
	04703M	Powder for I.V. infusion 60 mg	Early	3928	20111201	20121231
				4093	20121201	99990909
			Locally advanced	4083	20121201	99990909
06497Y		Powder for I.V. infusion 150 mg	Early	2419	20061001	20111231
				2420	20061001	20071031
				2421	20061001	20071031
				2422	20061001	20070331
				2599	20070401	20111231
07264H		Powder for I.V. infusion 60 mg	Early	3927	20111201	20121231
				4164	20121201	99990909
			Locally advanced	4142	20121201	99990909
07265J		Powder for I.V. infusion 60 mg	Early	3929	20111201	20121231
				4156	20121201	99990909
			Locally advanced	4104	20121201	99990909
07266K		Powder for I.V. infusion 60 mg	Early	3926	20111201	20121231
				4144	20121201	99990909
			Locally advanced	4143	20121201	99990909
07267L		Powder for I.V. infusion 60 mg	Early	3928	20111201	20121231
				4093	20121201	99990909
			Locally advanced	4083	20121201	99990909
09689Y		Powder for I.V. infusion 150 mg	Early	2419	20100701	20120430
				2599	20100701	20120430

Drug Name	Item Code	Form and Strength	Stage	Restriction Code	Start Date (yyyymmdd)	End Date (yyyymmdd)
	09690B	Powder for I.V. infusion 60 mg	Early	2419	20110201	20120430
				2599	20110201	20120430
	09691C	Powder for I.V. infusion 60 mg	Early	2419	20110201	20111231
				2599	20110201	20111231
	10269L	Powder for I.V. infusion 60 mg	Metastatic	5024	20150701	20150731
	10270M	Powder for I.V. infusion 60 mg	Metastatic	5024	20150701	20150731
	10296X	Powder for I.V. infusion 60 mg	Metastatic	5032	20150701	20150731
	10324J	Powder for I.V. infusion 60 mg	Grandfathering	5041	20150701	20150731
	10346M	Powder for I.V. infusion 60 mg	Metastatic	5032	20150701	20150731
	10362J	Powder for I.V. infusion 60 mg	Grandfathering	5041	20150701	20150731
	10381J	Powder for I.V. infusion 60 mg	Grandfathering	5041	20150801	99990909
	10383L	Powder for I.V. infusion 60 mg	Metastatic	5024	20150801	99990909
	10391X	Powder for I.V. infusion 60 mg	Metastatic	5032	20150801	99990909
	10401K	Powder for I.V. infusion 60 mg	Metastatic	5024	20150801	99990909
	10402L	Powder for I.V. infusion 60 mg	Metastatic	5032	20150801	99990909
	10423N	Powder for I.V. infusion 60 mg	Grandfathering	5041	20150801	99990909
	10682F	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Grandfathering	5041	20160401	20160630
			Early	6061	20160401	99990909
			Locally advanced	6062	20160401	99990909
			Metastatic	5024	20160401	20160630
	10721G	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Early	6059	20160401	99990909
			Locally advanced	6060	20160401	99990909
			Metastatic	5032	20160401	20160630
	10743K	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Grandfathering	5041	20160401	20160630
			Early	6061	20160401	99990909
			Locally advanced	6062	20160401	99990909
			Metastatic	5024	20160401	20160630
	10744L	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Early	6059	20160401	99990909
			Locally advanced	6060	20160401	99990909
			Metastatic	5032	20160401	20160630
	10798H	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Metastatic	5032	20160701	99990909
	10803N	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Metastatic	5024	20160701	99990909

Drug Name	Item Code	Form and Strength	Stage	Restriction Code	Start Date (yyyymmdd)	End Date (yyyymmdd)
	10811B	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Metastatic	5032	20160701	99990909
	10817H	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Metastatic	5024	20160701	99990909
	10825R	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Grandfathering	5041	20160701	99990909
	10829Y	Solution for subcutaneous injection containing trastuzumab 600 mg in 5 mL	Grandfathering	5041	20160701	99990909
TRASTUZUMAB EMTANSINE	10281D	Powder for I.V. infusion 100 mg	Grandfathering	4986	20150701	99990909
			Metastatic	4978	20150701	99990909
				4987	20150701	20160430
				6129	20160501	99990909
	10282E	Powder for I.V. infusion 100 mg	Grandfathering	4986	20150701	99990909
			Metastatic	4978	20150701	99990909
				4987	20150701	20160430
				6096	20160501	99990909
PERTUZUMAB	10267J	Solution for I.V. infusion 420 mg in 14 mL	Metastatic	5013	20150701	99990909
	10268K	Solution for I.V. infusion 420 mg in 14 mL	Grandfathering	5023	20150701	99990909
	10308M	Solution for I.V. infusion 420 mg in 14 mL	Metastatic	4971	20150701	99990909
	10309N	Solution for I.V. infusion 420 mg in 14 mL	Grandfathering	5023	20150701	99990909
	10333W	Solution for I.V. infusion 420 mg in 14 mL	Metastatic	4971	20150701	99990909
	10334X	Solution for I.V. infusion 420 mg in 14 mL	Metastatic	5013	20150701	99990909

Note: 99990909 indicates an open end date (i.e. restriction code was current in the 1 October 2017 PBS Schedule)