

## 7.10 PERTUZUMAB, Solution for IV infusion, 420mg in 14 mL, Perjeta<sup>®</sup>, Roche Products Pty Ltd

### 1 Purpose of Application

- 1.1 Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for pertuzumab for treatment of human epidermal growth factor receptor-2 positive (HER2+ positive), lymph node positive early breast cancer (eBC). The first submission was considered by the PBAC in July 2018.
- 1.2 The basis for listing was cost-effectiveness of pertuzumab in combination with trastuzumab and chemotherapy (Ptz+T+Chemo) compared to trastuzumab in combination with chemotherapy (T+Chemo).

**Table 1: Key components of the clinical issue addressed by the resubmission**

Component	Description
Population	Patients with HER2 positive, lymph node positive, eBC
Intervention	Pertuzumab in combination with trastuzumab and chemotherapy (Ptz+T+Chemo) for the adjuvant treatment of eBC for up to 52 weeks
Comparator	Trastuzumab in combination with chemotherapy (T+Chemo) for up to 52 weeks
Outcomes	Primary endpoint: iDFS Secondary endpoints: OS, RFI, DRFI, AEs Health-related QoL
Clinical claim	Ptz+T+Chemo is superior in terms of effectiveness compared with T+Chemo. Ptz+T+Chemo is inferior in terms of safety compared to T+Chemo.

AE: Adverse event; DRFI: Distant relapse-free interval; DFS: Disease-free survival; eBC: early breast cancer; HER2: human epidermal growth factor; iDFS: Invasive disease-free survival; OS: Overall survival; Ptz+T+Chemo: Pertuzumab in combination with trastuzumab and chemotherapy; QoL: Quality of Life; RFI: Relapse-free interval; T+Chemo: trastuzumab and chemotherapy.

Source: Table 1.1.1, p15 of the previous submission (no table presented in the resubmission).

### 2 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Amt	№.of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
PERTUZUMAB Solution for IV infusion, 840 mg 420mg in 14mL		0	Public, initial: \$6,229 published price \$ <span style="background-color: black; color: black;">██████</span> effective price  Private, initial: \$6,354 published price \$ <span style="background-color: black; color: black;">██████</span> effective price	Perjeta <sup>®</sup> , Roche Products Pty Ltd
<b>Category/Program</b>	Section 100 (Public/Private)– Efficient Funding of Chemotherapy			
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
<b>Severity:</b>	Early			
<b>Condition:</b>	HER2 positive breast cancer			
<b>PBS Indication:</b>	Early HER2 positive breast cancer			

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<b>Treatment phase:</b>	Initial treatment (3 weekly regimen)
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Clinical criteria:</b>	<p>Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) in the primary tumour, AND Patient must have evidence of lymph node status as demonstrated by a report documenting ≥1 positive node, AND Patient must commence treatment concurrently with adjuvant chemotherapy, AND Patient must commence treatment concurrently with trastuzumab, 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, AND Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy.</p>
<b>Administrative Advice:</b>	<p>Authority applications for initial treatment must be made in writing and 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 echocardiography (ECHO) or multigated acquisition (MUGA), prior to seeking the initial authority approval and then at 3 monthly intervals during treatment.</p>

Name, Restriction, Manner of administration and form	of Max. Amt	№.of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
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PERTUZUMAB Solution for IV infusion, 420 mg 420mg in 14mL	3	Public, continuing: \$3,157 published price \$ [redacted] effective price	Perjeta ®, Roche Products Pty Ltd
		Private, continuing: \$3,239 published price \$ [redacted] effective price	

<b>Category/Program</b>	Section 100 (Public/Private)– Efficient Funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Early
<b>Condition:</b>	HER2 positive breast cancer
<b>PBS Indication:</b>	Early HER2 positive breast cancer
<b>Treatment phase:</b>	Continuing treatment (3 weekly regimen)
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug, AND The treatment must be in combination with trastuzumab, AND</p>

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	<p>The treatment must not be used in a patient with a left ventricular ejection fraction (LVEF) of less than 45% and/or with symptomatic heart failure, AND Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy.</p>
Administrative Advice:	<p>A patient who has a treatment break of less than 6 weeks in PBS-subsidised treatment with this drug for reasons other than disease progression is eligible to continue to receive PBS-subsidised treatment with this drug.</p> <p>A patient who has a treatment break of more than 6 weeks in PBS-subsidised treatment with this drug is not eligible to receive PBS-subsidised treatment with this drug.</p> <p>Where a patient has had a treatment break the length of the break is measured from the date the most recent treatment was stopped to the date of the application for further treatment.</p> <p>Cardiac function must be tested by a suitable method including, for example, ECHO or MUGA, at 3 monthly intervals during treatment.</p>

<b>Category/Program</b>	Section 100 (Public/Private)– Efficient Funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Early
<b>Condition:</b>	HER2 positive breast cancer
<b>PBS Indication:</b>	Early HER2 positive breast cancer
<b>Treatment phase:</b>	Grandfathering treatment
<b>Restriction:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
Clinical criteria:	<p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition before [listing date] AND Patient must have evidence of lymph node status as demonstrated by a report documenting ≥1 positive node, 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, AND The treatment must be in combination with trastuzumab, AND Patient must not receive more than 52 weeks of combined PBS-subsidised and non-PBS-subsidised therapy. AND <i>Patient must have evidence of human epidermal growth factor receptor 2 (HER2) gene amplification as demonstrated by in situ hybridisation (ISH) in the primary tumour,</i> AND <i>Patient must have commenced non-PBS subsidised treatment concurrently with adjuvant chemotherapy,</i> AND <i>Patient must have commenced non-PBS subsidised treatment concurrently with trastuzumab</i> AND <i>Patient must have undergone surgery</i> AND <i>Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug</i></p>

Administrative Advice:	<p>Authority applications for treatment must be made in writing and must include a completed authority prescription form and a copy of the signed patient acknowledgement form.</p> <p>Cardiac function must be tested by echocardiography (ECHO) or multigated acquisition (MUGA), at 3 monthly intervals during treatment.</p>
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- 2.2 The resubmission proposed a PBS restriction that would restrict treatment to lymph node positive patients, which is unchanged from the previous submission. The TGA did not define “high risk of recurrence”. At its July 2018 meeting the PBAC accepted that the definition of “high risk patients” would include patients with lymph node positive status. Therefore, the PBAC considered it was reasonable to restrict pertuzumab to patients with HER2 positive eBC who have positive lymph node status (Public Summary Document (PSD), July 2018 PBAC meeting, item 6.10 pertuzumab, paragraph 2.1).
- 2.3 The restriction is changed from the previous submission and is largely consistent with that recommended by the PBAC (PSD, July 2018 PBAC meeting, item 6.10 pertuzumab, section 2). The exception being the baseline left ventricular ejection fraction (LVEF). The APHINITY trial excluded patients with a baseline LVEF <55%. The proposed PBS restriction in the previous submission excluded patients with a baseline LVEF <45% (consistent with the listing for trastuzumab) while the proposed PBS restriction in the current resubmission excluded patients with a baseline LVEF <50%. The PBAC previously considered it may be more appropriate to align the LVEF criterion for pertuzumab with the APHINITY criterion (PSD, July 2018 PBAC meeting, item 6.10 pertuzumab, paragraph 2.2). The resubmission stated that the proposed baseline LVEF <50% was based on Australian National Heart Foundation Cardiac Society guidelines and clinical expert opinion, and noted that the minimum LVEF values actually observed in APHINITY prior to commencement of treatment were 51% in the Ptz+T+Chemo arm, and 50% in the T+Chemo arm (CSR, page 205). The ESC noted that the change in LVEF is the clinically important measure, rather than the absolute value. Further, it was considered unlikely that clinicians would treat patients with serious cardiac disease/illness with pertuzumab, noting that these patients were excluded from the APHINITY trial. The ESC considered that on balance, it would be best to align the LVEF criteria with the current trastuzumab listing (LVEF <45%) to allow patients to be eligible for both drugs if they are to be used concurrently.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

### **3 Background**

#### ***Registration status***

- 3.1 Pertuzumab in combination with trastuzumab and chemotherapy was TGA registered on 4 September 2018 for the adjuvant treatment of patients with HER2 positive early breast cancer at high risk of recurrence.
- 3.2 The PBAC noted that pertuzumab in combination with trastuzumab and chemotherapy is also TGA approved for the neoadjuvant treatment of patients with

HER2-positive inflammatory or locally advanced, or early stage (either > 2 cm in diameter or node positive) breast cancer as part of a complete treatment regimen for early breast cancer.

***Previous PBAC consideration***

- 3.3 Pertuzumab was previously considered by the PBAC for the requested patient population at the July 2018 meeting. Table 2 summarises the outstanding matters of concern.

**Table 2: Summary of outstanding matters of concern**

Component	Matter of concern	How the resubmission addresses it
Registration status	A positive TGA Delegate's Overview available at the time of the Committee's consideration but the final circumstances of registration for use in the adjuvant setting was not known (paragraph 7.3).	Listed on the ARTG on 4 September 2018 Indication: Pertuzumab in combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2 positive early breast cancer at high risk of recurrence.
Clinical evidence	The PBAC considered that the comparative benefit of adding pertuzumab to the treatment of the subgroup of patients who were lymph node positive and HR+ was unknown. The PBAC considered it would have been informative to know the outcomes from this subgroup, as it represents a large group of patients who would seek PBS treatment (paragraph 6.28 and 7.7).	The resubmission argued that: "it is not possible to draw meaningful conclusions from a smaller, dual clinical characteristic lymph node positive and hormone receptor positive group, as this would entail exploratory analysis of a sub-group of a sub-group, involving minimal events and no statistical rigour. Further dissection would result in wide variability hence statistical conclusions are very limited, if not, impossible at this level." (p33 of the resubmission).
Clinical benefit	The PBAC was concerned that the modest benefit of adding pertuzumab to trastuzumab and chemotherapy was outweighed by the increased risk of AEs (in particular the cardiac risks and significant difference in experiencing diarrhoea), the uncertain magnitude of benefit in the HR+ lymph node positive patients and the uncertain place in therapy (paragraph 7.1).	The resubmission provided further information regarding: <ul style="list-style-type: none"> <li>• Whether the increase in iDFS is clinically meaningful, by comparing the results of previous trials of treatments for eBC, comparing the results to the ESMO MCBS, discussing the results with 21 Australian clinicians, and referencing a review by Hamelinck (2014).</li> <li>• The severity of cardiac risks and diarrhoea, by providing a more detailed analysis of the APHINITY trial results.</li> </ul>
ICER for the ITT population	While listing is proposed in the subgroup, without the ICER for the ITT population it was not possible to assess the impact on the cost-effectiveness of use in the broader population compared with the subgroup (paragraph 6.33 and 7.8).	The resubmission argued that it is irrelevant to assess the cost-effectiveness of Ptz+H+Chemo in the ITT population as this is not being sought for reimbursement. Whilst the ITT population was initially sought for TGA registration (with the initial PBAC submission occurring in parallel), the TGA has now finalised the indication for pertuzumab in 'high risk' patients (p60 of the resubmission).
Time horizon	The PBAC considered that use of the 50-year time horizon was overly long and reduced the reliability of the ICERs given the available trial follow-up and that there was no difference in OS (paragraph 6.43).	Time horizon reduced to 40 years (p59 of the resubmission).
Duration of treatment effect	The ESC considered that there was uncertainty around the duration of benefit and noted the ICER was highly sensitive to this. The PBAC agreed with the ESC's view and also noted the clinical evidence indicated modest benefits (paragraph 6.44).	Assumed that the treatment effect would remain until [redacted] years and then be [redacted] (changed from [redacted] to [redacted]) (p64 of the resubmission).
Extrapolation function	The ESC considered selection of the log-logistic function based on the pooled (summed) AIC, which forces common functional form, was not adequately justified in the submission. The PBAC agreed with the ESC's view and further noted that the application of the log-logistic function resulted in a lower ICER compared to the other parametric functions (paragraph 6.45).	Log-cumulative hazard plots were provided. The resubmission claimed that the [redacted] and therefore it is reasonable and appropriate methodologically to fit separate parametric functions to each treatment arm (p63 of the resubmission).

Component	Matter of concern	How the resubmission addresses it
Discount on trastuzumab	The PBAC noted that, as the sponsor of both pertuzumab and trastuzumab, a price reduction in [REDACTED], trastuzumab, was offered. The submission claimed that this would result in a cost-effective and budget neutral listing of pertuzumab (in combination with trastuzumab). However, the PBAC and its sub-committees were concerned that the cost-effectiveness of pertuzumab may not be maintained and the low net cost to Government may not be realised over time (PBAC ratified minutes paragraph 7.1 and 7.11).	The resubmission proposed a (p93 of the resubmission): <ul style="list-style-type: none"> <li>• [REDACTED]% discount on the price of pertuzumab for the proposed indication; and</li> <li>• [REDACTED]% discount on the price of trastuzumab for the proposed indication.</li> </ul> The discount on the price of trastuzumab is in addition to the (prospective) 25% price reduction on trastuzumab expected to occur due to future biosimilar market entry.
Method to estimate financial implications	DUSC considered that the submission had not justified the use of an epidemiological approach. DUSC considered i) the best available data to inform the utilisation of pertuzumab are PBS data for trastuzumab in the eBC setting; and ii) that a market share approach is the most appropriate method to derive the number of patients to be treated and the PBS cost-offsets associated with the listing of pertuzumab for eBC (paragraph 6.58).	Financial implications estimated using a market share approach.
Risk share	In addition, a risk share agreement would also be required to mitigate higher treatment uptake than estimated and use in patients who are not at high risk of disease recurrence (such as lymph node negative disease) (paragraph 7.12).	The resubmission proposed a cap on pertuzumab expenditure based on estimated use within the eligible population and specified by the proposed restriction (p95 of the resubmission).

AE: adverse event; ARTG: Australian Register of Therapeutic Goods; DUSC: drug utilisation subcommittee; eBC: early breast cancer; ESC: economics subcommittee; ESMO MCBS: European Society for Medical Oncology magnitude of clinical benefit scale; ICER: incremental cost-effectiveness ratio; HER2: human epidermal growth factor 2; HR: hormone receptor; ITT: intent to treat; LVEF: left ventricular ejection fraction; PBS: pharmaceutical benefits scheme; TGA: Therapeutic Goods Administration.

Source: Pertuzumab Public Summary Document (PSD) July 2018, PBAC ratified minutes, July 2018 PBAC meeting, 6.10 pertuzumab.

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

## 4 Population and disease

- 4.1 The proposed population and place of therapy of pertuzumab is unchanged from the previous submission.
- 4.2 Previously the PBAC was concerned that changes to the treatment of early breast cancer, such as the move towards neoadjuvant treatment, the use of shorter durations of treatment, dose dense chemotherapy regimens and neratinib may limit the applicability of the APHINITY trial results (PSD, July 2018 PBAC meeting, item 6.10 pertuzumab, paragraph 4.5 and 6.28). The PBAC also considered that the availability of trastuzumab emtansine (T-DM1) for patients with residual invasive disease at surgery after receiving neoadjuvant therapy may also change the treatment algorithm in the near future.
- 4.3 Neoadjuvant therapy: The PBAC noted that there is a move towards neoadjuvant therapy in patients with high risk eBC. This approach allows assessment of response to therapy at the time of surgery. A recent large meta-analysis of eBC trials with

neoadjuvant chemotherapy<sup>1</sup> reported the prognostic importance of pathological complete response (pCR), which correlates with event free and overall survival (OS). The current extent of neoadjuvant treatment in Australia is unknown. Patients receiving neoadjuvant treatment were excluded from the APHINITY trial. The PBAC noted that no data were presented demonstrating the clinical benefit of pertuzumab after neoadjuvant treatment.

- 4.4 Shorter duration (6 months) trastuzumab: The resubmission argued that several trials demonstrated inferior efficacy with trastuzumab with durations of treatment less than 12 months (Pivot 2013, Mavroudis 2015, Conte 2018 and Joensuu 2018). The resubmission also argued that 12 months of trastuzumab treatment is consistent with international guidelines, with advice from Australian clinicians (N=21), and with the duration of trastuzumab in Australia and the APHINITY trial. The ESC considered it was reasonable that most patients would undergo 12 months of trastuzumab treatment as this is what is currently accepted as standard of care.
- 4.5 Dose dense chemotherapy: The resubmission acknowledged that there is evidence supporting dose dense chemotherapy reducing disease recurrence (Gray 2017). However, the resubmission argued that dose dense chemotherapy serves as a supplement to targeted therapies, and does not preclude nor substitute for targeted therapy. The resubmission noted Australian clinicians (N=21) considered that the clinical place of Ptz+T+Chemo upon PBS listing for the treatment of eBC is unlikely to change as a result of the ongoing body of evidence evaluating dose dense chemotherapy (and that such regimens can be prescribed in combination with targeted therapy). The ESC considered although the treatment algorithm may be unaffected by the use of dose dense chemotherapy, the use of dose dense chemotherapy in clinical practice may reduce the applicability of the APHINITY trial results. Dose dense chemotherapy was administered in ██████% of APHINITY patients receiving anthracycline-based therapy. The extent of use of dose dense chemotherapy in Australia is unknown and therefore the ESC considered this to be an applicability issue, although noted it is not possible to quantify the impact of this issue.
- 4.6 Neratinib (extended adjuvant setting): The resubmission argued that Australian clinicians (N=21) considered that pertuzumab was more convenient than neratinib as it did not extend the treatment duration and can be administered on the same day as trastuzumab, and that the extended duration of treatment with neratinib was associated with toxicities. The ESC noted that use of neratinib may reduce the applicability of the trial results in that where patients would otherwise be treated with neratinib following T+Chemo, the absolute reduction in iDFS is likely to be reduced. The PBAC noted that patients receiving neratinib were excluded from the APHINITY trial and no data were presented assessing the efficacy of both pertuzumab and

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<sup>1</sup>Spring L, et al: Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival, stratified by breast cancer subtypes and adjuvant chemotherapy usage. 2018 San Antonio Breast Cancer Symposium. Abstract GS2-03. Presented December 5, 2018.

neratinib in the adjuvant treatment of eBC, therefore the benefit of sequential use of these treatments is unknown.

- 4.7 Trastuzumab emtansine (T-DM1): The PBAC noted that the results from a trial<sup>2</sup> assessing T-DM1 in patients with residual invasive disease after completing neoadjuvant chemotherapy + trastuzumab support a change in the treatment pathway and that T-DM1 may become an alternative treatment to pertuzumab in the adjuvant setting.

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

## **5 Comparator**

- 5.1 The resubmission nominated trastuzumab plus chemotherapy (T+Chemo) as the main comparator. This is unchanged from the previous submission and was considered reasonable by the PBAC (PSD, July 2018 PBAC meeting, item 6.10 pertuzumab, paragraph 7.4).
- 5.2 The ESC agreed that neratinib could be considered a near market comparator if the PBAC does not consider it appropriate for patients to be administered Ptz+T+Chemo in Year 1 followed by neratinib in Year 2. The PBAC considered that neratinib is a relevant near market comparator because, without evidence of the clinical benefit for sequential treatment with neratinib after pertuzumab, sequential use is not considered to be appropriate.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from an individual (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments supported the submission for pertuzumab for the adjuvant treatment of HER2 positive, lymph node positive eBC, which is a cancer subtype with a high risk of disease recurrence. The comments also noted that pertuzumab for this indication can currently be accessed privately in the neoadjuvant and adjuvant setting but had a high financial impact on patients. A comment noted that the side effects of pertuzumab included diarrhoea and a low neutrophil count which impacted on chemotherapy treatment but the side effects were outweighed by the reduction in cancer recurrence.
- 6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) in support of PBS listing pertuzumab for patients with HER2 positive, lymph node

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<sup>2</sup> von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med.* 2019 Feb 14;380(7):617-628. doi: 10.1056/NEJMoa1814017.

positive eBC. The PBAC specifically noted that the BCNA advised it would have liked the submission to have also sought a listing in the neoadjuvant setting.

- 6.4 The Medical Oncology Group of Australia (MOGA) included Ptz+T+Chemo in the category of “high priority for PBS listing”, on the basis of improved disease free survival in the APHINTY trial, but noting that the OS benefit was immature. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for Ptz+T+Chemo, which was grade A (out of A, B and C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies)<sup>3</sup>, based on a comparison with T+Chemo.

### **Clinical trials**

- 6.5 The resubmission was based on one head-to-head randomised trial comparing Ptz+T+Chemo (anthracycline or docetaxel plus carboplatin) to T+Chemo (anthracycline or docetaxel plus carboplatin) (N=4,804): APHINITY. This is unchanged from the previous submission. The resubmission did not present longer-term follow-up data.
- 6.6 Table 3 presents the details of the trial presented in the resubmission.

**Table 3: Trial and associated reports presented in the resubmission**

<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
APHINITY (NCT01358877)	APHINITY Primary Clinical Study Report – BIG 4-11 / BO25126 / TOC4939g. Report No. 1075429. (Clinical Appendix)	July 2017
	von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer.	NEJM 2017; 377:122-131
	von Minckwitz. APHINITY trial (BIG 4-11): A randomised comparison of chemotherapy (C) plus trastuzumab (T) plus placebo (Pla) versus chemotherapy plus trastuzumab (T) plus pertuzumab (P) as adjuvant therapy in patients (pts) with HER2-positive early breast cancer (EBC).	Journal of Clinical Oncology. 2017;35(15)
	von Minckwitz G, Baselga J, Bradbury I et al. Adjuvant pertuzumab and herceptin in initial therapy of breast cancer: APHINITY (BIG 4-11/BO25126/TOC4939g).	Cancer Research. 2011; 71(24).

Source: Table 2.2.1, p43 of the previous submission.

- 6.7 The key features of the direct randomised trial are summarised in Table 4.

<sup>3</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Ptz + T + Chemo vs T + Chemo</b>						
APHINITY	4,805	R, DB 45 mths	Low	HER2+ eBC	iDFS (primary outcome) OS, recurrence-free interval (RFI), distant RFI (DRFI), EORTC QLQ-C30 and EQ-5D-3L	iDFS used in economic model

DB:double blind; DRFI: distant recurrence free interval; EORTC:European organisation for research and treatment of cancer; iDFS: invasive disease-free survival; OS: overall survival; R: randomised; RFI: recurrence free interval; QLQ: quality of life questionnaire  
Source: p44, p51, p52, p57 and p92 of the previous submission.

6.8 The ESC noted the primary composite outcome iDFS did not align with the STEEP guidelines<sup>4</sup> (standardised definitions of breast cancer clinical trial end points) in that the APHINITY trial excluded second primary non-breast cancers. While this can affect effectiveness estimates, it did not appear to affect the results when comparing outcomes that included and did not include non-breast cancers in the APHINITY trial (pp4124-4125 of CSR APHINITY BO25126a.pdf). The ESC noted that future references or comparisons with clinical data should be clear about the iDFS definition in the clinical trials presented.

### Comparative effectiveness

6.9 Table 5 presents the results of the ITT analysis and Table 6 presents the result of the sub-group analysis. The trial results are unchanged from the previous submission.

Table 5: Results of primary and secondary efficacy outcomes (ITT) at 3 years: time-to-event data

Outcome	Ptz+T+Chemo (N=2,400)		T+Chemo (N=2,404)		RD	P value (log rank test)	HR (95% CI)
	n/N with event (%)	Median time to event (95% CI)	n/N with event (%)	Median time to event (95% CI)			
<b>Primary outcome</b>							
iDFS	171/2,400 (7.1%)	NA	210/2,404 (8.7%)	NA	-1.6%	<b>0.0446</b>	<b>0.81</b> (0.66, 1.00)
<b>Secondary outcomes</b>							
OS	80/2,400 (3.3%)	NA	89/2,404 (3.7%)	NA	-0.4%	0.4673	0.89 (0.66, 1.21)
RFI	138/2,400 (5.8%)	NA	173/2,404 (7.2%)	NA	-1.4%	<b>0.0430</b>	<b>0.79</b> (0.63, 0.99)
DRFI	119/2,400 (5.0%)	NA	145/2,404 (6.0%)	NA	-1.1%	0.1007	0.82 (0.64, 1.04)

CI= confidence interval; DRFI= distant recurrence free interval; HR= Hazard Ratio iDFS= invasive disease-free survival; n= number of participants reporting data; N= total participants in group; OS= overall survival; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; RD= risk difference; RFI= recurrence free interval; T+Chemo= trastuzumab and chemotherapy.

Note: Bold indicates a statistically significant difference.

Source: Table 2.5.1, p61 of the previous submission and calculated during evaluation

<sup>4</sup> Hudis et al (2007) 'Proposal for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System', *Journal of Clinical Oncology*, 25, no. 15, pp 2127-2132  
< <http://ascopubs.org/doi/full/10.1200/JCO.2006.10.3523>>

**Table 6: Results of subgroup analysis with ITT results and complement results at 3 years: time-to-event data**

Population	Ptz+T+Chemo n with event/N (%)	T+Chemo n with event/N (%)	Hazard ratio (95% CI)
<b>iDFS (primary outcome)</b>			
ITT population	171/2,400 (7.1%)	210/2,404 (8.7%)	0.81 (0.66, 1.00)
Identified subgroup (lymph node positive)	139/1,503 (9.2%)	181/1,502 (12.1%)	<b>0.77 (0.62, 0.96)</b>
Complement of subgroup (lymph node negative)	32/897 (3.6%)	29/902 (3.2%)	1.13 (0.68, 1.86)
Test for treatment effect variation	–	–	P = [REDACTED]
<b>Overall survival (secondary outcome)</b>			
ITT population	80/2,400 (3.3%)	89/2,404 (3.7%)	0.89 (0.66, 1.21)
Identified subgroup (lymph node positive)	[REDACTED]/1,503 ([REDACTED]%)	[REDACTED]/1,502 ([REDACTED]%)	[REDACTED] ([REDACTED], [REDACTED])
Complement of subgroup (lymph node negative)	[REDACTED]/897 ([REDACTED]%)	[REDACTED]/902 ([REDACTED]%)	[REDACTED] ([REDACTED], [REDACTED])
Test for treatment effect variation	–	–	P = [REDACTED]
<b>RFI (secondary outcome)</b>			
ITT	138/2,400 (5.8%)	173/2,404 (7.2%)	0.79 (0.63, 0.99)
Identified subgroup (lymph node positive)	117/1,503 (7.8%)	153/1,502 (10.2%)	<b>0.77 (0.60, 0.98)</b>
Complement of subgroup (lymph node negative)	[REDACTED]/897 (2.3%)	[REDACTED]/902 ([REDACTED]%)	[REDACTED] ([REDACTED], [REDACTED])
Test for treatment effect variation	–	–	P = [REDACTED]
<b>DRFI (secondary outcome)</b>			
ITT	119/2,400 (5.0%)	145/2,404 (6.0%)	0.82 (0.64, 1.04)
Identified subgroup (lymph node positive)	[REDACTED]/1,503 ([REDACTED]%)	[REDACTED]/1,502 ([REDACTED]%)	[REDACTED] ([REDACTED], [REDACTED])
Complement of subgroup (lymph node negative)	[REDACTED]/897 ([REDACTED]%)	[REDACTED]/902 ([REDACTED]%)	[REDACTED] ([REDACTED], [REDACTED])
Test for treatment effect variation	–	–	P = [REDACTED]

CI= confidence interval; DRFI= distant recurrence free interval; iDFS= invasive disease-free survival; n= number of participants reporting data; N= total participants in group; OS= overall survival; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; RFI= recurrence free interval; T+Chemo= trastuzumab and chemotherapy.

Note: Bold indicates a statistically significant difference.

Source: Table 2.6.1, p70 of the previous submission pscr

- 6.10 The iDFS event-free rates for node-positive patients were 91.99% vs. 90.15% at 3 years (difference of 1.84%) and 89.88% vs. 86.68% at 4 years (difference of 3.2%), for Ptz+T+Chemo versus T+Chemo, respectively (ITT population).
- 6.11 The improvement in OS was not statistically significant in the intent to treat (ITT) population (P=0.4673) or in the lymph node positive subgroup (P=not reported). The Pre-Sub-Committee Response (PSCR) argued that the benefits in the curative adjuvant setting occur over a long time horizon, with trastuzumab trials not showing a statistically significant improvement in OS at 3 and 4 years but showing a statistically significant improvement after 10-11 years. The pre-PBAC response also noted mature OS data will not be available until approximately 2023. The ESC considered that OS benefit for pertuzumab may be seen over time, as for trastuzumab, however this benefit has not yet been demonstrated.
- 6.12 The ESC noted that distant recurrence could be considered a more patient-relevant outcome. However, the ESC noted that the outcome of distant recurrence was not statistically significant, noting that it was a secondary outcome in the APHINITY trial.
- 6.13 The resubmission did not present a subgroup analysis of patients who were lymph node positive and HR positive, as previously requested by the PBAC. The PSCR reiterated that it was not possible to draw meaningful conclusions from this smaller patient population and suggested that limiting treatment to the entire node positive patient population would allow clinicians adequate scope to assess the potential

benefit for patients with HR+ or HR- status. The ESC considered that the magnitude of clinical benefit in the HR+ patient population remains uncertain, but noted that the node positive population included a substantial proportion of HR+ patients.

6.14 The resubmission provided further information to show that the APHINITY trial results are clinically meaningful. In particular, the resubmission argued that:

- The incremental benefit provided by Ptz+T+Chemo for HER2 positive, lymph node positive eBC patients (3.2% at four years) is comparable to advancements offered by previous new therapies involved in the evolution of eBC therapy and further progress the treatment for eBC. The ESC noted that the trial outcomes presented in Table 7 were different to the APHINITY trial. The ESC acknowledged that the addition of an extra therapy is likely to result in smaller incremental benefit compared with a new treatment modality. The ESC questioned whether the comparison was valid given the differences in outcomes and considered it did not substantially add to the ESC's confidence that the results from APHINITY were clinically meaningful.
- The ESMO MCBS for Ptz+T+Chemo compared to T+Chemo would be Grade A [out of Grade A to C, with Grade A representing the grade with substantial improvement], based on the lower limit of the confidence interval of the hazard rate ratio in the lymph node positive patients (which is < 0.65). The ESC noted that the ESMO MCBS grade of A for pertuzumab supported the clinical meaningfulness of the iDFS benefit for pertuzumab, based on the current evidence but agreed with the evaluation that the ESMO MCBS score for pertuzumab for eBC may fall to Grade B with the availability of OS data if the absolute difference in OS is similar to that observed with iDFS.
- Australian clinicians (N=21) considered that the results observed in APHINITY were clinically meaningful and the change was very significant from the patient's perspective. The ESC considered the methodology used in conducting this survey was unclear and therefore the significance of the opinions presented was uncertain.
- Hamelinck (2014) concluded that most patients judged small to moderate benefits sufficient to consider adjuvant systemic therapy worthwhile. More specifically, the study found that the minimum increase in the overall survival rate that participants considered worthwhile was: between 0.1% to 7% at 5 years for chemotherapy; and between 2% to 10% at 5 years for hormonal therapy. In comparison, the increase in OS for Ptz+T+Chemo (0.3% at 3 years) was not statistically significant compared to T+Chemo in lymph node positive patients at 3 years. The ESC agreed with evaluator that the incremental benefit at 3 years in OS from APHINITY is potentially less than the minimum increase considered meaningful at 5 years in the review. The ESC also noted that the number of studies included in the review was small.

**Table 7: Comparison of APHINITY trial results to efficacy gains from introduction of new eBC treatment modalities**

	<b>INTRODUCTION of a new treatment modality</b>	<b>IMPROVEMENT of existing / second generation modality</b>	
<b>Chemotherapy</b>	<b>CMF vs. no chemo (EBCTCG 2012, meta-analysis of 123 trials)</b>	<b>Anthracycline vs. CMF (EBCTCG 2012, meta- analysis of 123 trials)</b>	<b>Taxane + anthracycline vs. anthracycline (EBCTCG 2012, meta- analysis of 123 trials)</b>
Absolute benefit <sup>a</sup>	+9.9%	+3.2%	+3.6%
Risk ratio (95% CI)	0.70 (0.63, 0.77)	0.89 (0.82, 0.96)	0.84 (0.78, 0.91)
<b>Endocrine therapy</b>	<b>Tamoxifen vs. no tamoxifen (HR+) (EBCTCG 2011, meta-analysis of 20 trials)</b>	<b>Aromatase Inhibitor vs. tamoxifen (EBCTCG 2015, meta-analysis of 9 trials)</b>	
Absolute benefit <sup>a</sup>	+12.3%	+3.1%	
Risk ratio (95% CI)	0.61 (0.57, 0.65)	0.80 (0.73, 0.88) (should be 0.80, 0.68-0.93)	
<b>Anti-HER2 therapy</b>	<b>T+Chemo vs. Chemo<sup>b</sup> (Slamon 2011, BCIRG-006 trial)</b>	<b>Ptz+T+Chemo vs. T+Chemo<sup>c</sup> (APHINITY trial)</b>	
Absolute benefit	+5.9% +6.0% to +9.0%	+3.2% <sup>f</sup>	
Hazard ratio (95% CI)	0.76 (0.68, 0.86) 0.64 (0.53, 0.78) <sup>d</sup> 0.75 (0.63, 0.90) <sup>e</sup>	0.77 (0.62, 0.96) <sup>g</sup>	

CI: confidence interval; CMF: cyclophosphamide, methotrexate, fluorouracil; HR+: =hormone receptor positive

a: improvement in recurrence rate at 5 years; b: DFS benefit; c: iDFS benefit; d: AC-TH; e: TCH; f: iDFS at 4 years (lymph-node positive);

g: lymph-node positive

Source: Figure 2.1.2, p35 of the resubmission

6.15 The PSCR and pre-PBAC response restated that in the curative setting, any significant improvement in the risk of recurrence versus the standard of care is clinically meaningful. The ESC considered that the uncertainty around the clinical significance of the overall benefits gained with Ptz+T+Chemo treatment remained, despite the additional information provided in the resubmission.

## Comparative harms

6.16 Table 8 presents a summary of patient-relevant harms, based on the APHINITY trial. This is unchanged from the previous submission.

**Table 8: Summary of key adverse events in the randomised trial**

Trial ID	Ptz+T+Chemo n with event/N (%)	T+Chemo n with event/N (%)	RR (95% CI)
Any AE <sup>a</sup>	2361/2364 (99.9%)	2393/2405 (99.5%)	<b>1.004 (1.001, 1.007)</b>
Grade $\geq$ 3 AE	1518/2364 (64.2%)	1379/2405 (57.3%)	<b>1.120 (1.070, 1.172)</b>
SAE	692/2364 (29.3%)	585/2405 (24.3%)	<b>1.203 (1.095, 1.322)</b>
AEs leading to treatment discontinuation	309/2364 (13.1%)	277/2405 (11.5%)	1.135 (0.975, 1.321)
AEs leading to dose modification/interruption	1217/2364 (51.5%)	1064/2405 (44.2%)	<b>1.164 (1.096, 1.235)</b>
Treatment-related AEs (HER2 targeted)	█/2364 (█%)	█/2405 (█%)	█ (█, █)
AEs leading to death	10/2364 (0.4%)	14/2405 (0.6%)	0.727 (0.323, 1.633)
Total deaths	73/2364 (3.1%)	95/2405 (4.0%)	0.782 (0.579, 1.055)
Treatment-related deaths	1/2364 (0.0)%	1/2405 (0.0%)	1.017 (0.064, 16.256)

AE: adverse event; CI: confidence interval; n: number of participants reporting data; N: total participants in group; Ptz+T+Chemo: Pertuzumab in combination with trastuzumab and chemotherapy; SAE: serious adverse event; T+Chemo: trastuzumab and chemotherapy. Note: Bold indicates a statistically significant difference.

a: Includes deaths for patients that had no AEs; 1 patient had a death without any AE in the Placebo arm

Source: Table 2.5.2, p64 of the previous submission

6.17 Regarding cardiac risk the resubmission argued that:

- Less than 1% of the 4,805 patients treated in APHINITY experienced a primary cardiac event. This occurred primarily in patients receiving an anthracycline-based treatment, and all patients had at least one risk factor for heart disease. Despite this, heart failure was reversible and the majority of patients experiencing a primary cardiac event recovered, irrespective of treatment received. While this was verified as true, █ of 17 patients who experienced a primary cardiac event with Ptz+T+Chemo had either died, resolved with sequelae or had not resolved at the clinical cut-off date. In comparison this was the case for █ of 7 patients treated with T+Chemo. Consequently, for some patients the impact of cardiac toxicity on their quality of life will be ongoing. The ESC agreed with the evaluation that the consequences of the cardiac events in the pertuzumab arm indicated that they were likely to be clinically meaningful.
- Less than 3% of the 4,805 patients treated in APHINITY experienced a secondary cardiac event. This occurred primarily in patients receiving an anthracycline-based treatment, and overall, the majority of patients experiencing a secondary cardiac event recovered, irrespective of treatment received. The majority of patients with cardiac dysfunction were asymptomatic and have shown improvement or return to baseline function on follow-up, in line with the experience with trastuzumab. The cardiac side-effect profile appears to be similar to that of trastuzumab, and combination of the two antibodies has not increased the rate of cardiac events in

patients studied. The ESC considered this to be reasonable, noting that the trial excluded patients with any significant cardiac history.

- There was minimal change in LVEF measurements over time in both treatment arms, regardless of the chemotherapy regimen received. The mean LVEF values remained above 60% for the majority of patients throughout the study. The ESC considered that this appears reasonable but noted that patients with significant cardiac history were excluded from the APHINITY trial.

6.18 Overall, the ESC considered the evidence provided in the resubmission supported the claim that the cardiac risks experienced for patients treated with Ptz+T+Chemo were manageable. However, the ESC noted that the additional cardiac events for patients treated with pertuzumab, without complete resolution, are likely to have a long term impact on patient quality of life and may result in downstream effects on the health care system.

6.19 Regarding diarrhoea the resubmission stated that:

- ████% of patients treated with Ptz+T+Chemo required treatment with loperamide and fluid plus electrolyte replacement compared to ████% of patients treated with T+Chemo.
- 9.9% of patients treated with Ptz+T+Chemo experienced grade  $\geq 3$  diarrhoea compared to 3.7% of patients treated with T+Chemo.
- 2.5% of patients treated with Ptz+T+Chemo experienced a serious AE of diarrhoea (defined as fatal, life threatening, requires or prolongs inpatient hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or was considered a significant medical event by the investigator) compared to 0.7% of patients treated with T+Chemo. None were grade 5 (fatal).
- ████% of patients treated with Ptz+T+Chemo experienced diarrhoea that necessitated treatment withdrawal compared to ████% of patients treated with T+Chemo.
- The highest incidence was reported during the (taxane) chemotherapy treatment period, with a marked decrease upon chemotherapy cessation.

6.20 The PSCR argued that clinicians are experienced in managing Ptz+T+Chemo in patients with mBC and that the AE of diarrhoea is not a particular concern of clinicians as it is manageable and time limited. The ESC noted the incidence of diarrhoea remains high with Ptz+T+Chemo and regardless of whether it is chemotherapy-induced, patients treated with pertuzumab were more likely to experience diarrhoea. The ESC also

advised that early intervention with loperamide and electrolyte replacement may be required.

### Benefits/harms

6.21 A summary of the comparative benefits for Ptz+T+Chemo versus T+Chemo in lymph node positive patients and the comparative harms for the safety population is presented in Table 9. This is unchanged compared to the previous submission.

**Table 9: Summary of comparative benefits and harms for Ptz+T+Chemo and T+Chemo in lymph node positive patients and safety analysis population**

Time-to-event outcome: APHINITY						
	Ptz+T+Chemo	T+Chemo	Absolute difference	HR (95% CI)		
<b>iDFS (lymph node positive patients)</b>						
Event, n/N (%)	139/1,503 (9.2%)	181/1,502 (12.1%)		0.77 (0.62, 0.96)		
Median iDFS (months)	NR	NR	NA			
iDFS at 3 years, % (95% CI)	92.0% (90.6, 93.4)	90.2% (88.6, 91.7)	1.8%			
iDFS at 4 years, % (95% CI)	89.9% (not reported)	86.7% (not reported)	3.2%			
<b>OS (lymph node positive patients)</b>						
Deaths n/N (%)	█/1,503 (█%)	█/1,502 (█%)		█ (█, █)		
Median (months)	█	█	█			
OS at 3 years, % (95% CI)	█ (█)	█ (█)	█%			
<b>Harms (safety analysis population)</b>						
	Ptz+T+Chemo n/N	T+Chemo n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)*
				Ptz+T+Chemo	T+Chemo	
<b>Grade ≥3 AE</b>						
APHINITY	1518/2364 (64.2%)	1379/2405 (57.3%)	1.12 (1.07, 1.172)	64.2	57.3	6.9% (4.1%, 9.6%)*
<b>SAE</b>						
APHINITY	692/2364 (29.3%)	585/2405 (24.3%)	1.203 (1.095, 1.322)	29.3	24.3	4.9% (2.4%, 7.5%)*
<b>Grade ≥3 AE diarrhoea</b>						
APHINITY	108/2364 (4.6%)	28/2405 (1.2%)	3.924 (2.6, 5.923)	4.6	1.2	3.4% (2.5%, 4.3%)*
<b>SAE diarrhoea</b>						
APHINITY	58/2364 (2.5%)	18/2405 (0.7%)	3.278 (1.938, 5.546)	2.5	0.7	1.7% (1.0%, 2.4%)*

\* Median duration of follow-up: APHINITY = 45 months

AE= Adverse event; CI= confidence interval; HR= hazard ratio; iDFS= invasive disease free survival; OS= overall survival; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; RD= risk difference; RR= relative risk; SAE= serious adverse event; T+Chemo= trastuzumab and chemotherapy; NA= not available; NR= not reached

Source: Table 2.5.1, p61, Table 2.5.2, p64, Table 2.5.4 p67, Table 2.5.5 p68, and Table 2.6.1 p70 of the previous submission, the CSR and calculated during the evaluation.

6.22 On the basis of direct evidence presented by the submission, for every 100 patients, with involvement of ≥1 positive lymph nodes, treated with Ptz+T+Chemo in comparison to T+Chemo:

- At 3 years:
  - Approximately 2 additional patients would not experience recurrence (return of invasive disease).

- No difference in overall survival.
- Over a median duration of follow-up of 45 months:
  - Approximately 7 additional patients would experience a grade  $\geq 3$  AE.
  - Approximately 5 additional patients would experience a SAE.
  - Approximately 3 additional patients would experience grade  $\geq 3$  diarrhoea, defined as having  $\geq 8$  diarrhoea episodes per day, possibly requiring hospitalisation.
  - Approximately 2 additional patients would experience a SAE of diarrhoea.

### ***Clinical claim***

6.23 The clinical claim was unchanged from the previous submission:

- Ptz+T+Chemo is superior in terms of effectiveness compared with T+Chemo in patients with HER2 positive, lymph node positive eBC.
- Ptz+T+Chemo is inferior in terms of safety compared to T+Chemo.

6.24 Previously the PBAC considered that:

- The claim of superior comparative effectiveness was reasonable but questioned whether the modest benefit demonstrated in the trial was clinically meaningful (PSD, July 2018 PBAC meeting, item 6.10 pertuzumab, paragraph 6.24).
- The claim of inferior safety was reasonable and was supported by the data (paragraph 6.26).

6.25 Overall, previously the PBAC was concerned that the modest benefit of adding pertuzumab to trastuzumab and chemotherapy was outweighed by the increased risk of AEs (in particular the cardiac risks and significant difference in experiencing diarrhoea), the uncertain magnitude of benefit in the HR+ lymph node positive patients and the uncertain place in therapy (paragraph 7.1). The ESC and the PBAC considered, despite the additional information presented in the resubmission, the same uncertainties remain as the benefit to harm ratio was essentially unchanged from the previous submission.

### ***Economic analysis***

6.26 The submission presented a stepped economic evaluation which compared Ptz+T+Chemo with T+Chemo, based on the APHINITY trial as well as external data sources and implemented a modelled evaluation. The type of economic evaluation presented was a cost-utility analysis.

6.27 Table 10 summarises the key components of the economic evaluation, focusing on the key differences with the previous submission. The ESC noted that errors in the previous submission around discounting and transition from first line to second line mBC were identified and corrected in the resubmission.

**Table 10: Summary of model structure and rationale**

Component	Summary
Time horizon	40 years in the model base case versus 45 months in the APHINITY trial. This is reduced from 50 years in the previous submission. The revised time horizon is consistent with the time horizon applied in the 2006 trastuzumab PBAC submission <sup>5</sup> .
Outcomes	LYG and QALYs gained
Methods used to generate results	Markov model
Health states	iDFS, Locoregional Recurrence, Remission, Distant Recurrence (1 <sup>st</sup> line mBC)*, Distant Recurrence (2 <sup>nd</sup> line mBC)**, Death
Cycle length	1 week
Transition probabilities	<p>iDFS to locoregional recurrence or the distant recurrence health states: APHINITY trial iDFS Kaplan-Meier data (lymph node positive patients) extrapolated from 45 months (median follow up time) to lifetime (40 years) by fitting separate log-logistic parametric functions to the APHINITY data. This is unchanged from the previous submission.</p> <p><u>Remission to distant recurrence (1<sup>st</sup> line mBC):</u> constant transition probability per cycle derived from Hamilton et al (2015). This is unchanged from the previous submission. The Hamilton study analysed retrospective data sets collected during 1989 to 2005 from four different centres. The submission assumed that the median time progressing from remission to distant recurrence was ■ years (from Hamilton) and applied an exponential function to estimate the weekly transition probability. The rate of distant recurrence from remission may have changed since this study due to changes in treatment patterns. The assumption of a constant rate of transition from remission may not be clinically reasonable, however given the limited data provided in Hamilton this approach appears reasonable.</p> <p><u>Distant recurrence (1st line mBC, early progressors) to (2nd line mBC, early progressors) and death:</u> constant transition probability per cycle based on EMILIA trial (T-DM1 arm).</p> <p><u>Distant recurrence (1st line mBC, late progressors) to (2nd line mBC, late progressors) and death:</u> constant transition probability per cycle based on CLEOPATRA trial.</p> <p>The EMILIA and CLEOPATRA trials were previously considered by the PBAC for the PBS listing of T-DM1<sup>6</sup> and pertuzumab<sup>7</sup> for mBC, respectively. This is unchanged from the previous submission. It is unknown whether the use of pertuzumab for eBC will reduce the effectiveness of pertuzumab for mBC. Sensitivity analysis was not conducted on this assumption. The PSCR (p3) argued that non-clinical studies have revealed that the anti-tumour activity of pertuzumab and trastuzumab do not lead to loss of HER2 expression on tumour cells (Scheuer 2009). The ESC noted this claim was based on human xenograph tumour models. The efficacy of Ptz+T+Chemo in mBC, after treatment with Ptz+T+Chemo in eBC, remains uncertain without human trial data. The trial results were applied using a constant transition probability based on an exponential function, rather than applying the Kaplan-Meier data and extrapolated using a parametric function. Of note, in the previous PBAC submissions for mBC, a gamma function was fitted to both EMILIA and CLEOPATRA trials. Using different parametric functions (except Weibull function) had limited impact on the ICERs for both drugs in the previous submissions. Using an exponential function simplifies the model, especially for the mBC setting. However, exponential parametric function may not be the best fit for the Kaplan-Meier curve and may lead to biased results. The direction of bias is unknown as sensitivity analysis was not conducted on the results presented in this re-submission. The ESC considered that extrapolation in the model introduced uncertainty as much of the assumed benefit in the model comes from the extrapolated proportion of the model.</p>

<sup>5</sup> PBAC (October 2006) Public Summary Document: Trastuzumab, powder for I.V. infusion, 150 mg, Herceptin®, Roche Products Pty Ltd

<sup>6</sup> PBAC (March 2014) Public Summary Document - Trastuzumab emtansine, injections, 100 mg vial and 160 mg vial, Kadcyla®, Roche Products Pty Ltd

<sup>7</sup> PBAC (March 2014) Public Summary Document – Pertuzumab, 420 mg/14 mL injection, 1 x 14 mL vial Perjeta®, Roche Products Pty Ltd

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Component	Summary
	<p><u>Transition probabilities from iDFS, locoregional recurrence, remission to death</u>: a constant transition probability based on pooled mortality data from the APHINITY trial and background mortality (whichever is higher). This is unchanged from the previous submission and is reasonable.</p> <p><u>Duration of treatment effect</u>: It was assumed that the treatment effect is null from [redacted] years. This is changed from the previous submission, which assumed that the treatment effect [redacted] to [redacted] with no treatment effect after [redacted] years. Previously the PBAC considered that the treatment effect may endure beyond five years, but there was uncertainty around the duration of benefit (PSD, July 2018 PBAC meeting, item 6.10 pertuzumab, paragraph 6.44).</p>
Resource use and costs	<p>Cost of therapies was changed compared to the previous submission:</p> <ul style="list-style-type: none"> <li>- The cost of pertuzumab was lower compared to the previous submission due to the application of a [redacted]% price discount.</li> <li>- The cost of trastuzumab when administered concomitantly with pertuzumab was [redacted] compared to the previous submission. While a 10% statutory price reduction on 1 June 2018 and an assumed further 25% price discount due to the future entry of a biosimilar were applied, the submission applied a lower price discount of [redacted]% (compared to [redacted]% from the previous submission).</li> <li>- The cost of trastuzumab when NOT administered concomitantly with pertuzumab was [redacted] compared to the previous submission due to a 10% statutory price reduction on 1 June 2018 and the resubmission assumed a further 25% price discount due to the future entry of a biosimilar.</li> </ul> <p>The assumption made in terms of the proportion of patients who receive each of the subsequent therapies was not justified and introduces uncertainty.</p> <p>The proportions of patients experiencing grade ≥3 AEs (sheet- Adverse Event Cost in Economic Evaluation.xlsx) were inconsistent with the data reported in the CSR (Table 54, p187 of the CSR). However, the ICER was not sensitive to the rates of AEs.</p> <p>The submission may have underestimated the dosage and therefore cost of trastuzumab and T-DM1 given that the average weight of Australian HER2+ eBC patients is [redacted]kg (p72 of the submission). However, the ICER was not sensitive to the average weight of the target Australian women.</p> <p>No cost was applied to the remission health state. No justification was provided. This may underestimate costs as patients may receive subsequent specialist visits and CT scans to confirm the disease has not returned.</p>
Utilities	<p>iDFS (on treatment), iDFS (off treatment), locoregional recurrence and remission health states used EQ-5D-3L data from the APHINITY trial and valued using the Australian weights for the general population estimated by Viney et al. (2011).</p> <p>Distant recurrence: Lloyd 2006</p> <p>2<sup>nd</sup> line mBC: Lloyd 2006</p> <p>These are reasonable.</p>

AE: adverse event; ICER: incremental cost-effectiveness ratio; iDFS: Invasive disease free survival; LYG: life years gained; mBC: metastatic breast cancer; QALYs: Quality adjusted life years; Ptz+T+Chemo: Pertuzumab in combination with trastuzumab and chemotherapy; T+Chemo: trastuzumab and chemotherapy; T-DM1: trastuzumab emtansine

\* Distant Recurrence (1st line mBC) consists of two health states: Distant Recurrence (1st line mBC, early progressors) and Distant Recurrence (1st line mBC, late progressors).

\*\* Distant Recurrence (2nd line mBC) consists of two health states: Distant Recurrence (2nd line mBC, early progressors) and Distant Recurrence (2nd line mBC, late progressors).

Source: Table 3.1.1, p58 of the resubmission and compiled during the evaluation.

6.28 The ESC noted that a high proportion of the overall cost offsets were from the subsequent treatment costs in patients with distant recurrence and second line mBC (see Table 12 below). The ESC noted that the recurrence treatment costs for patients

in the distant recurrence and 2<sup>nd</sup> line mBC states were applied every cycle until death. This resulted in implausibly high costs for the treatment of distant recurrence and 2<sup>nd</sup> line mBC. For example, the total cost for treating a distant recurrence (>18 months) was estimated to be \$[REDACTED]. However, the model estimated a cost of \$[REDACTED] (undiscounted) for treating distant recurrence (>18 months) for P+T+Chemo and \$[REDACTED] (undiscounted) for T+Chemo. These costs suggest each patient treated with P+T+Chemo experiences an average of [REDACTED] ( $\frac{\$[REDACTED]}{\$[REDACTED]}$ ) distant recurrence events, which is inconsistent with the modelled number of events ([REDACTED]). Similarly, for T+Chemo, patients would need to experience an average of [REDACTED] ( $\frac{\$[REDACTED]}{\$[REDACTED]}$ ) recurrence events and this is inconsistent with the modelled number of events (0.55). To correct this, subsequent therapy costs were applied as a once-off cost with the cost calculated based on the duration of treatment as per the existing RSA for pertuzumab ([REDACTED] months) and T-DM1 ([REDACTED] months). The ICER increased from dominant to less than \$15,000 per QALY.

- 6.29 Table 11 shows the results of the stepped analysis. The submission did not present the stepped analysis using the discounted pertuzumab and trastuzumab prices, the relevant prices were only introduced at step 8. The stepped analysis was compiled with the relevant requested prices during the evaluation. The results of the economic evaluation in Tables 12 and 13 have been updated using the corrected recurrence treatment costs. In the pre-PBAC response the sponsor maintained that the subsequent treatment costs have been appropriately calculated and applied in the model and that costs applied at each cycle represent the apportioned cost for the proportion of patients newly transitioning to this health state.
- 6.30 The ESC noted that the cost for management of AEs appears lower than would be expected, though it is uncertain what impact this would have on the ICER.

Table 11: Results of the stepped economic evaluation

Step and component	Ptz+T+Chemo	T+Chemo	Increment	Increment with █% discount on pertuzumab	Increment with █% discount on pertuzumab and █% discount on trastuzumab*
<b>Step 1: trial-based costs and outcomes (up to █ months)</b>					
Costs	\$ █	\$ █	\$ █	\$ █	\$ █
LYG	█	█	█	█	█
QALYG	█	█	█	█	█
Incremental cost/extra LYG gained			\$ █	\$ █	\$ █
Incremental cost/extra QALYG gained			\$ █	\$ █	\$ █
<b>Step 2: parametric extrapolation from 45 months over lifetime horizon (to 40 years)</b>					
Costs	\$ █	\$ █	\$ █	\$ █	-\$ █
LYG	█	█	█	█	█
QALYG	█	█	█	█	█
Incremental cost/extra LYG gained			\$ █	\$ █	Dominant
Incremental cost/extra QALYG gained			\$ █	\$ █	Dominant
<b>Step 3 (application of time limited treatment effect)</b>					
Costs	\$ █	\$ █	\$ █	\$ █	\$ █
LYG	█	█	█	█	█
QALYG	█	█	█	█	█
Incremental cost/extra LYG gained			\$ █	\$ █	\$ █
Incremental cost/extra QALYG gained			\$ █	\$ █	\$ █
<b>Step 4 (incorporation of MRU costs)</b>					
Costs	\$ █	\$ █	\$ █	\$ █	\$ █
LYG	█	█	█	█	█
QALYG	█	█	█	█	█
Incremental cost/extra LYG gained			\$ █	\$ █	\$ █
Incremental cost/extra QALYG gained			\$ █	\$ █	\$ █
<b>Step 5 (incorporation of AE related costs)</b>					
Costs	\$ █	\$ █	\$ █	\$ █	\$ █
LYG	█	█	█	█	█
QALYG	█	█	█	█	█
Incremental cost/extra LY gained			\$ █	\$ █	\$ █
Incremental cost/extra QALY gained			\$ █	\$ █	\$ █
<b>Step 6 (incorporation of utility values for QALYs) – unchanged from Step 5</b>					
<b>Step 7 (inclusion of end of life costs)</b>					
Costs	\$ █	\$ █	\$ █	\$ █	\$ █
LYG	█	█	█	█	█
QALYG	█	█	█	█	█
Incremental cost/extra LY gained			\$ █	\$ █	\$ █
Incremental cost/extra QALY gained			\$ █	\$ █	\$ █
<b>Step 8 (inclusion of █% discount on pertuzumab and █% discount on trastuzumab)*</b>					
Costs	\$ █	\$ █	\$ █		
LYG	█	█	█		
QALYG	█	█	█		
Incremental cost/extra LY gained			\$ █		

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Step and component	Ptz+T+Chemo	T+Chemo	Increment	Increment with █% discount on pertuzumab	Increment with █% discount on pertuzumab and █% discount on trastuzumab*
Incremental cost/extra QALY gained (base case)			\$ █		
<b>Previous submission (Step 9: inclusion of proposed RSA to achieve a dominant ICER and budget neutrality) (Price discount =121.04%)</b>					
Costs	\$ █	\$ █	-\$ █		
LYG	█	█	█		
QALYG	█	█	█		
Incremental cost/extra LY gained			Dominant		
Incremental cost/extra QALY gained			Dominant		

AE= adverse events; ICER= incremental cost-effectiveness ratio; iDFS= invasive disease free survival; LYG: life years gained; mBC= metastatic breast cancer; MRU= medical resource use; Ptz+T+Chemo= Pertuzumab in combination with trastuzumab and chemotherapy; QALYG= quality adjusted life years gained; RSA= risk share agreement; T+Chemo= trastuzumab and chemotherapy.

\*Plus a further 25% price reduction to account for biosimilar entry

Source: Table 3.8.1, p72 of the resubmission and compiled during the evaluation using the current economic model (economic evaluation.xlsx) and the economic model for the previous submission (economic evaluation.xlsx). Updated results accounting for corrected subsequent treatment costs were calculated during the ESC evaluation. Subsequent therapy costs were applied as a once off cost with the cost calculated based on the duration of treatment consistent as per the existing risk sharing arrangement (RSA) for pertuzumab (█ months) and T-DM1 (█ months).

Table 12: Health care resource items: disaggregated summary of cost impacts (base case ■■■% price discount applied to pertuzumab and ■■■% price discount applied to trastuzumab in the Ptz+T+Chemo arm)

Resource item	Ptz+T+Chemo	T+Chemo	Incremental cost
<b>Pharmaceutical products</b>			
Pertuzumab	\$■■■	0	\$■■■
Trastuzumab	\$■■■	\$■■■	-\$■■■
Total	\$■■■	\$■■■	-\$■■■
<b>Administration</b>			
IV infusion	\$■■■	\$■■■	-\$■■■
<b>Medical Resource Use*</b>			
MRU on treatment	\$■■■	\$■■■	-\$■■■
MRU off treatment	\$■■■	\$■■■	-\$■■■
Total	\$■■■	\$■■■	-\$■■■
<b>Management of adverse events*</b>			
Neutropenia	\$■■■	\$■■■	-\$■■■
Febrile Neutropenia	\$■■■	\$■■■	-\$■■■
Neutrophil Count Decreased	\$■■■	\$■■■	-\$■■■
Ejection Fraction Decreased	\$■■■	\$■■■	-\$■■■
Diarrhoea	\$■■■	\$■■■	-\$■■■
Total	\$■■■	\$■■■	-\$■■■
<b>Subsequent line therapies (episodes of care)</b>			
Locoregional recurrence	\$■■■	\$■■■	-\$■■■
Distant recurrence (1 <sup>st</sup> line early and late progressors)	\$■■■	\$■■■	-\$■■■
2nd line mBC (early and late progressors)	\$■■■	\$■■■	-\$■■■
Total	\$■■■	\$■■■	-\$■■■
End of life cost	\$■■■	\$■■■	-\$■■■
<b>Overall total*</b>	<b>\$■■■</b>	<b>\$■■■</b>	<b>-\$■■■</b>

\*The proportion of patients experiencing grade ≥3 AEs (sheet- Adverse Event Cost in Economic Evaluation.xlsx) were inconsistent with the data reported in the CSR (Table 54, p187 of the CSR).

MRU= medical resources use, including CT Scan, LVEF assessment – ECHO, Subsequent specialist visit, Haematology and serum chemistry (complete blood count, differential and platelet count), Blood chemistry and urinalysis test (biochemistry, electrolytes, renal and liver function tests)

Source: Results in Economic Evaluation.xlsx. Updated results accounting for corrected subsequent treatment costs were calculated during the ESC evaluation.

**Table 13: Disaggregated summary of health outcomes included in the economic evaluation**

Outcome	Ptz+T+Chemo	T+Chemo	Incremental outcome
iDFS at 5 years	█████%	█████%	█████%
LYG	█████	█████	█████
QALYs – iDFS	█████	█████	█████
QALYs – locoregional recurrence	█████	█████	█████
QALYs – Remission	█████	█████	█████
QALYs - Distant recurrence, 1st line (early progressors)	█████	█████	█████
QALYs – Distant recurrence, 2nd line mBC (early progressors)	█████	█████	█████
QALYs - Distant recurrence, 1st line (late progressors)	█████	█████	█████
QALYs – Distant recurrence, 2nd line mBC (late progressors)	█████	█████	█████
<b>Total QALYs</b>	█████	█████	█████

iDFS= Invasive disease free survival; mBC: metastatic breast cancer; QALYs= Quality adjusted life years.

Source: compiled during the evaluation based on sheet Result of Economic Evaluation.xlsx

- 6.31 The costs of pertuzumab were █████ compared to the previous submission due to the █████% price discount applied (compared to █████% in the previous submission), while the █████ cost-saving from trastuzumab with Ptz+T+Chemo was due to the █████% price discount applied (compared to a █████% price discount in the previous submission). Conversely, the █████ cost-saving from subsequent therapies was due to the shorter time horizon, the █████ duration of the treatment effect and correcting the approach for applying the treatment costs for recurrence.
- 6.32 The estimated LYG (█████) and QALYs gained (█████) were less than the previous submission (█████ LYG and █████ QALYs gained). This was mainly due to a reduction in the time horizon and a █████ in the duration of the treatment effect. The ESC considered that the inclusion of an OS gain in the model may be inappropriate as there was no statistically significant benefit demonstrated for pertuzumab.
- 6.33 The number of recurrence events over the 45-month trial follow-up period and over the 40-year model time horizon are compared in Table 14. The ESC noted a large number of events were modelled to occur more than 45 months after the commencement of adjuvant therapy. For distant recurrence, the number of events avoided with the addition of pertuzumab approximately doubled (from █████ per █████ patients to █████ per █████ patients) with the time horizon extended from 45 months to 40 years. Over the 40-year time horizon each patient treated with Ptz+T+Chemo gained █████ life years (or █████ life years gained per █████ people). Thus, there were █████ (█████/█████) life years gained per distant recurrence avoided. This highlights, in the model, treatment with pertuzumab is assumed to prevent, rather than delay, recurrence.

Table 14: Disaggregated summary of health outcomes (patients with distant and local recurrence) included in the economic evaluation

Outcome	Ptz+T+Chemo	T+Chemo	Incremental outcome (per 100 patients)
LY (40 years, undiscounted)	█	█	█
<b>Distant recurrence</b>			
Trial distant recurrence (45 months) <sup>a</sup>	█ %	█ %	█
Model distant recurrence (40 years) <sup>a</sup>	█ %	█ %	█
<b>Local recurrence</b>			
Trial local recurrence (45 months) <sup>b</sup>	█ %	█ %	█
Model local recurrence (40 years) <sup>b</sup>	█ %	█ %	█

LY= life years.

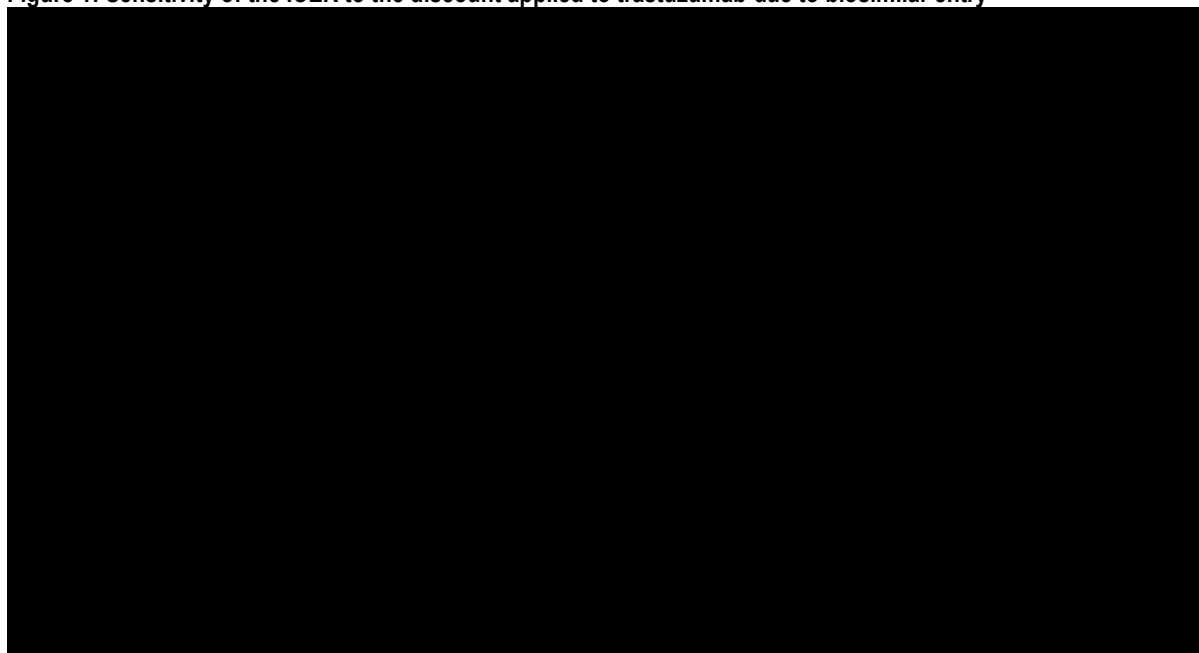
a Sum of columns T, U and AB of sheet PH and columns R, S and Z of sheet H up to 45 months (trial) and 40 years.

b sum of column V for sheet PH and T for sheet H up to 45 months (trial) and 40 years.

Source: compiled for the ESC based on sheets "Result" for undiscounted LY, "KMIDFS" for trial distant and local recurrence, "H" and "PH" for model distant and local recurrence of Economic Evaluation.xlsx

- 6.34 The ICER does not change substantially even if the time horizon is reduced to 10 years (less than \$15,000/QALY with subsequent treatment costs corrected). With a shorter time horizon the difference across the treatment groups in the number of recurrence events is larger and hence the cost offset for subsequent treatments is larger. Thus with a shorter time horizon the incremental costs are reduced as well as the incremental benefits.
- 6.35 Previously the PBAC considered that the pertuzumab treatment effect may endure beyond five years, but there was uncertainty around the duration of benefit (PSD, July 2018 PBAC meeting, item 6.10 pertuzumab, paragraph 6.44). The base case analysis assumed a treatment effect for █ years. If the treatment effect was reduced to 5 years the ICER increased to less than \$15,000/QALY.
- 6.36 The ICER was sensitive to the discount applied to trastuzumab due to biosimilar entry (see Figure 1) and sensitive to the discount applied to trastuzumab due to the listing of pertuzumab (i.e. the reduction in addition to the 25% discount applied upon biosimilar entry). The ICER associated with treatment with Ptz+T+Chemo compared to T+Chemo for HER2 positive lymph node positive eBC was estimated to be \$45,000 to \$75,000 per QALY with a █% discount on trastuzumab, once subsequent treatment costs were corrected. The ESC noted that the ICER increased if the trastuzumab price reduction from entry of biosimilars was larger than 25% because cost offsets from trastuzumab were reduced i.e. the █% trastuzumab price reduction due to the listing of pertuzumab was applied to a lower price and hence was less. The PBAC noted that the base case ICER presented in the submission relied on the trastuzumab discount offered and would also be affected by the entry of trastuzumab biosimilars.

Figure 1: Sensitivity of the ICER to the discount applied to trastuzumab due to biosimilar entry



Source: Compiled during the evaluation using Economic Evaluation.xlsx.

### ***Drug cost/patient/course***

6.37 The drug cost per patient per course was estimated to be \$ [REDACTED]. This was based on an effective AEMP per vial of \$ [REDACTED], assuming 33% of patients are public and 67% are private patients, and one loading dose (two vials) and 16 continuing doses are received.

### ***Estimated PBS usage & financial implications***

6.38 This submission was not considered by DUSC. The resubmission took a market share approach to estimate the number of scripts for pertuzumab based on published sources and clinician surveys. The ESC considered this was appropriate, noting that the resubmission changed this from an epidemiological approach from the previous submission to align with the DUSC's previous recommendation.

6.39 Table 15 presents the estimated use and financial implications.

Table 15: Estimated use and financial implications

	2019	2020	2021	2022	2023	2024
<b>Estimated extent of use</b>						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed*	█	█	█	█	█	█
<b>Estimated financial implications of pertuzumab + trastuzumab**</b>						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Estimated financial implications for trastuzumab***</b>						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$ █ #	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS/DHS/other	\$0	\$0	\$0	\$0	\$0	\$0
Net cost to PBS/RPBS/MBS/DHS	\$ █ #	\$ █	\$4 █	\$ █	\$ █	\$ █
<b>Net financial implications without 25% price discount on trastuzumab due to biosimilar entry</b>						
Net cost to PBS/RPBS/MBS/DHS	\$ █ #	\$ █	\$ █	\$ █	\$ █	\$ █

\* Based on the number of scripts for trastuzumab (3-weekly) for eBC 2017-2018 (31,984), projected using growth rates of the incidence of breast cancer (1.01%), and adjusted for lymph node status (█%) and uptake (█%)

\*\* A █% price discount was proposed. Also assumes future biosimilar entry (25% reduction).

\*\*\* Assumes future biosimilar entry (25% reduction).

# includes a one off cost for █ grandfathered Ptz+H+Chemo patients of \$ █ in year one of listing; numbers may not compute exactly due to rounding

Source: Table 4.4.1, p85 of the resubmission

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.40 Overall, it was estimated that there would be a net cost to Government of \$30 to \$60 million over six years. The net cost of pertuzumab for eBC is likely to be overestimated as it included treatment for locally advanced breast cancer. Conversely, the estimate does not account for reduced use of pertuzumab and trastuzumab for mBC. The net cost did not account for cost-savings due to recurrence, hence why the ICER was dominant but there was an estimated net financial implication for the Government. The ESC noted that not including the recurrence costs in the estimates, which are a significant cost offset in the economic evaluation, created uncertainty in the financial estimates.

### Quality Use of Medicines

6.41 The resubmission did not include a quality use of medicines section.

6.42 The previous submission stated that it would undertake standard medical affairs activities, such as supporting breast cancer conferences, organising pertuzumab and eBC education meetings and providing online materials to ensure clinicians are well

equipped to commence their HER2 positive, lymph node positive, eBC patients on Ptz+T+Chemo. The risk management program proposed as part of the pertuzumab in eBC registration approval will be conducted as agreed with the TGA.

- 6.43 The previous submission noted that there are no post-marketing surveillance studies being conducted involving pertuzumab for the adjuvant treatment of eBC. There is a need to understand the use of pertuzumab and the risk of AEs in the wider population. However, the previous submission noted that there are several other ongoing trials involving pertuzumab for eBC. The APHINITY trial also plans to follow-up patients for 10 years.

### **Financial Management – Risk Sharing Arrangements**

- 6.44 In addition to the [REDACTED]% discount on pertuzumab, the resubmission proposed a [REDACTED]% discount on the AEMP of all PBS items for 3 weekly trastuzumab for eBC (4650R, 4703M, 7266K, 7267L, 10682F, 10721G, 10743K, 10744L) for the proposed indication (when used in combination with pertuzumab for the treatment of HER2 positive lymph node positive eBC patients). The resubmission did not explain what would occur if more than one biosimilar is listed.
- 6.45 This is changed from the previous submission, which proposed a [REDACTED]% discount on all PBS items for 3 weekly trastuzumab for eBC (4650R, 4703M, 7266K, 7267L, 10682F, 10721G, 10743K, 10744L) to achieve a [REDACTED]% discount on the ex-manufacturer price of trastuzumab when used in combination with pertuzumab for HER2 positive lymph node positive eBC patients.
- 6.46 For pertuzumab, the [REDACTED]% discount would be administered via a confidential rebate arrangement on the ex-manufacturer price (AEMP per vial = \$3,072.37; 420 mg).
- 6.47 For trastuzumab, the [REDACTED]% discount would also be administered via a confidential rebate arrangement if a biosimilar of trastuzumab is not PBS listed. If a biosimilar of trastuzumab is PBS listed, then the listed and effective price of trastuzumab would take into account both the 25% and [REDACTED]% reductions for the proportion of trastuzumab use in the HER2 positive lymph node positive eBC. In order to implement the proposed [REDACTED]% trastuzumab price reduction the proportion of use in HER2 positive, lymph node positive eBC compared with other trastuzumab indications would need to be estimated. In the pre-PBAC response the sponsor indicated that [REDACTED]% represents the proportion of eBC that is HER2 positive and lymph node positive, however this would be only a proportion of the total trastuzumab market. The PSCR clarified that the availability of one or more biosimilars of trastuzumab would not change the proposed pricing and RSA that provides surety to the cost-effectiveness of Ptz+H+Chemo over time. Should (one or more) biosimilars of trastuzumab be PBS listed, this would result in trastuzumab moving from the F1 to the F2 formulary, whereby the list and effective prices would be the same. Furthermore, the trastuzumab molecule would be subject to price disclosure arrangements, potentially further reducing its price over time. As noted above, the ICER increases with larger price reductions resulting from the listing of trastuzumab biosimilars.

- 6.48 The resubmission proposed a cap on pertuzumab expenditure based on estimated use within the eligible population and specified by the proposed restriction. Further details on what the expenditure cap would be were not provided.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the Section 100 (Efficient Funding of Chemotherapy), Authority Required listing of pertuzumab in combination with trastuzumab and chemotherapy (Ptz+T+Chemo) for the adjuvant treatment of HER2 positive, lymph node positive early breast cancer (eBC). The PBAC considered that the clinical place for pertuzumab in the adjuvant setting is unclear, given the shift toward treating high-risk patients in the neoadjuvant setting and the lack of data for adjuvant pertuzumab following neoadjuvant treatment. The PBAC's concerns remained regarding the small benefit with the addition of pertuzumab in terms of invasive disease free survival (with overall survival (OS) data pending). The PBAC maintained the view that the small benefit needed to be balanced against the increased risk of adverse events (AEs) and the impact of additional treatment infusions on both patients and the health care system. The PBAC considered that the ICER for pertuzumab remained uncertain because much of the assumed benefit in the model relied on extrapolation of outcomes and external data sources, and the base case ICER was dependent on a reduction in the cost of trastuzumab. However, as in the previous consideration, the PBAC's concerns regarding the sponsor's price proposal were secondary to its concerns about the extent of clinical benefit with pertuzumab and its clinical place in eBC therapy.
- 7.2 The PBAC considered the clinical place in therapy for pertuzumab for HER2 positive, lymph node positive eBC is unclear. The PBAC noted that there is a move towards neoadjuvant therapy in patients with high-risk HER2+ eBC. This was supported by an Australian breast cancer consumer group which highlighted that pertuzumab's place in therapy is changing and its use in the neoadjuvant setting is becoming more widely recommended for women with HER2 positive eBC. The PBAC noted that a neoadjuvant approach allows assessment of response to therapy at the time of surgery. A recent large meta-analysis of eBC trials with neoadjuvant chemotherapy reported the prognostic importance of pathological complete response (pCR), which correlates with event free survival and OS. The PBAC also noted that the results from a trial assessing T-DM1 in patients with residual invasive disease after completing neoadjuvant chemotherapy + trastuzumab support a change in the treatment pathway and that T-DM1 may become an alternative treatment to pertuzumab in the adjuvant setting.
- 7.3 The PBAC noted that Ptz+T+Chemo is currently TGA registered for the adjuvant treatment of patients with HER2 positive eBC at high risk of recurrence (which aligns with the submission's requested PBS listing). The PBAC also noted that Ptz+T+Chemo is TGA registered for the neoadjuvant treatment of patients with HER2-positive inflammatory or locally advanced, or early stage (either > 2 cm in diameter or node

- positive) breast cancer as part of a complete treatment regimen for early breast cancer, however a PBS listing has not been requested for this use. Patients receiving neoadjuvant treatment were excluded from the APHINITY trial, and this impacts on the applicability of the trial results to clinical practice.
- 7.4 The PBAC maintained its view that trastuzumab plus chemotherapy (T+Chemo) as the main comparator was appropriate. The PBAC also noted that both neratinib and T-DM1 could be considered near market comparators and the place of pertuzumab would need to be considered with regard to potential changes in the clinical algorithm.
- 7.5 The clinical evidence presented in the resubmission was unchanged from the previous submission. The PBAC noted that the submission was based on a well-designed placebo-controlled randomised trial (APHINITY) comparing Ptz+T+Chemo to T+Chemo, where the chemotherapy regimen was an anthracycline or docetaxel plus carboplatin.
- 7.6 The PBAC noted the iDFS event-free rates for node-positive patients were 91.99% vs. 90.15% at 3 years (difference of 1.84%) and 89.88% vs. 86.68% at 4 years (difference of 3.2%), for Ptz+T+Chemo versus T+Chemo, respectively. The PBAC maintained that the magnitude of absolute benefit was small. The improvement in OS was not statistically significant in the ITT population ( $P=0.4673$ ) or in the lymph node positive subgroup ( $P$ =not reported). The PSCR argued that the benefits in the curative adjuvant setting occur over a long time horizon, with trastuzumab trials not showing a statistically significant improvement in OS at 3 and 4 years but showing a statistically significant improvement after 10-11 years. The PBAC agreed with the ESC's view that an OS benefit for pertuzumab may be seen over time, as was seen for trastuzumab, however this benefit has not yet been demonstrated.
- 7.7 The PBAC noted that patients treated with Ptz+T+Chemo had a significantly higher risk of grade  $\geq 3$  AEs (RR=1.12, 95% CI: 1.07, 1.17), serious AEs (SAEs) (RR=1.20, 95% CI: 1.10, 1.32), Grade  $\geq 3$  diarrhoea (RR=3.92, 95%CI: 2.60, 5.92), and a SAE of diarrhoea (RR=3.28, 95% CI: 1.94, 5.55). This was unchanged from the previous submission.
- 7.8 The PBAC maintained its view that the claim of superior comparative effectiveness was reasonable in terms of the risk of recurrence (iDFS) but considered that the magnitude of benefit was small. The PBAC considered the claim of inferior safety was reasonable and was supported by the data. The PBAC maintained its view that despite the additional information presented in the resubmission, as no new clinical data were provided, the same uncertainties remain as the benefit to harm ratio was essentially unchanged from the previous submission.
- 7.9 The submission presented a cost-utility analysis (stepped economic evaluation) which compared Ptz+T+Chemo with T+Chemo, based on the results of the lymph node positive subgroup from the APHINITY trial and external data sources.
- 7.10 The estimated LYG ( ) and QALYs gained ( ) were less than the previous submission ( LYG and QALYs gained). This was mainly due to a reduction in the time horizon and a in the duration of the treatment effect. The ESC

noted a large number of events were modelled to occur more than 45 months after the commencement of adjuvant therapy, i.e. after the trial follow up period. The PBAC noted that in the AFFINITY trial there was no statistically significant difference in OS (with up to 45 months of follow up). However, the model, when extrapolated to 40 years, generated an additional [REDACTED] life years with Ptz+T+Chemo compared with T+Chemo. The PBAC considered that the inclusion of an OS gain in the model was highly uncertain given there was no statistically significant benefit demonstrated for pertuzumab in the APHINITY trial.

- 7.11 The PBAC noted ESC's concern regarding the high cost offsets due to a reduction in the use of subsequent treatments for distant recurrence and second line mBC. The PBAC considered that the correction to the model where subsequent therapy costs were applied as a once-off cost based on the duration of treatment as per the existing RSAs for pertuzumab ([REDACTED] months) and T-DM1 ([REDACTED] months) was appropriate. This increased the ICER from dominant to less than \$15,000 per QALY.
- 7.12 Overall, the PBAC noted that much of the assumed benefit in the model, such as the OS gain and distant recurrences avoided, were not based on data from the APHINITY trial but relied on extrapolation and external data sources. As a result, the PBAC considered that the ICER for pertuzumab remained uncertain. In addition, the PBAC noted that the cost-effectiveness of pertuzumab remained uncertain given that the ICER was dependent on a reduction in the cost of trastuzumab which would be affected by the entry of trastuzumab biosimilars. The ICER was estimated to be \$45,000 to \$75,000 per QALY with a [REDACTED]% discount on trastuzumab, once subsequent treatment costs were corrected.
- 7.13 The PBAC considered the market share approach to estimate the number of scripts for pertuzumab was appropriate. It was estimated that there would be a net cost to Government of \$30 to \$60 million over six years. The net cost did not account for cost-savings due to reduced recurrences, and this explained the apparent anomaly of a dominant ICER but a net financial cost for the Government. The PBAC agreed with the ESC's advice that not including the recurrence costs in the estimates, which are a significant cost offset in the economic evaluation, created uncertainty with the financial estimates. Overall, the PBAC considered the proposed net financial cost to government was high, particularly given the small magnitude of benefit of pertuzumab.
- 7.14 The PBAC advised that any future resubmission would need to be a major resubmission and would need to address the PBAC's concerns about the clinical place for pertuzumab, taking into account the shift toward neoadjuvant treatment, and the PBAC's concerns regarding the magnitude of clinical benefit for Ptz+T+chemo, particularly in terms of the OS benefit. In light of the changing treatment landscape of early stage HER2+ breast cancer in the neoadjuvant setting and the emerging data available in this area, the PBAC would welcome a submission for trastuzumab emtansine (T-D1M), which is another medicine that is sponsored by Roche.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

**8 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.

**9 Sponsor's Comment**

The sponsor had no comment.