

**5.05 PALBOCICLIB,  
Capsule 75 mg, 100 mg and 125 mg,  
Ibrance<sup>®</sup>, Pfizer Australia Pty Ltd.**

**1 Purpose of Application**

1.1 The submission requested an Authority Required listing for palbociclib in combination with a non-steroidal aromatase inhibitor (NSAI) (letrozole or anastrozole) as initial endocrine-based therapy in postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC).

**2 Requested listing**

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

Name, Restriction, Manner of administration and form	Max. Qty	Nº. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PALBOCICLIB Capsule 75 mg, 100 mg, 125 mg	21	5	Listed: \$ [REDACTED] Effective: \$ [REDACTED]	Ibrance <sup>®</sup> Pfizer Australia

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<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>	Advanced
<b>Condition:</b>	<del>Advanced</del> breast cancer
<b>PBS Indication:</b>	Advanced breast cancer
<b>Treatment phase:</b>	<del>Initial and continuing</del>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	<del>The treatment must be in combination with a non-steroidal aromatase inhibitor (letrozole or anastrozole) as initial endocrine-based therapy.</del> <i>The treatment must be in combination with a non-steroidal aromatase inhibitor AND The treatment must be an initial endocrine-based therapy for this condition.</i>
<b>Clinical criteria:</b>	The condition must be hormone receptor positive, AND The condition must be human epidermal growth factor receptor 2 (HER2) negative.
<b>Population criteria:</b>	<del>The</del> Patient must be postmenopausal.

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<p><b>Prescriber Instructions: (Included in LI)</b></p>	<p>Authority applications for initial treatment must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed [TBA] - PBS Supporting Information Form which includes: (i) a copy of the pathology reports from an Approved Pathology Authority confirming the presence of hormone receptor and lack of presence of HER2 gene amplification by in situ hybridisation (ISH); and (ii) a copy of the signed patient acknowledgement form.</p>
<p><b>Administrative Advice: (not included in LI)</b></p>	<p>No applications for increased maximum quantities will be authorised. No applications for increased repeats will be authorised. Special Pricing Arrangements apply. Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a> Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

2.2 The submission also requested that the PBAC consider:

- Whether patients who are currently well-managed with a NSAI (letrozole or anastrozole) should also be able to access the addition of palbociclib to their NSAI regimen at the time of PBS-listing (a prevalent pool of patients). The ESC noted that evidence of benefit in this patient population is not available.
- Whether men with breast cancer should also be able to access the addition of palbociclib to their NSAI regimen at the time of PBS-listing. There is no evidence available regarding the use of palbociclib in men which accounts for <1% of all breast cancers. DUSC noted that the size of the male population with metastatic (stage IV) breast cancer was very small. The ESC and DUSC noted the PBAC's previous November 2014 recommendation to amend the PBS restrictions for five endocrine therapies for breast cancer to allow males to access subsidised treatment, when the criteria 'The patient must be postmenopausal' was replaced with 'Patient must not be pre-menopausal'.

2.3 The proposed PBS restriction is not in line with the proposed TGA indication or the trial population. The key differences are:

- Concomitant chemotherapy: letrozole was the only NSAI tested with palbociclib in the trials. The Pre-Sub-Committee-Response (PSCR) (p. 1) stated that, although the proposed restriction is not in line with the TGA indication, Australian oncologists have highlighted the importance of being able to use palbociclib concomitantly with letrozole or anastrozole and indicated that extending the usage to anastrozole may be considered during registration with the TGA. The ESC considered that, on balance in clinical practice, it would be reasonable to expect that letrozole or anastrozole would provide a similar benefit in combination with palbociclib. The therapeutic relativity sheets state that anastrozole, for the treatment of advanced breast cancer in post-menopausal women, was recommended on a cost minimisation basis compared to letrozole.
- Ceasing treatment upon progression: treatment was ceased upon progression in the trials. This condition was not included in the proposed PBS restriction. In the PSCR (p. 1), the sponsor welcomed the inclusion of a clause to restrict treatment

upon progression. The ESC agreed that the inclusion of this restriction matched the clinical trial protocol, but noted that there remained a risk of continuing use post-progression.

- Hormonal status: The trials only included patients with ER+, HER2- status. The ESC noted that the indication in the draft Product Information was for patients with hormone receptor positive disease, but TGA evaluation was ongoing.
- ECOG performance status: In PALOMA-1 and PALOMA-2 patients were required to have an ECOG performance status 0-1, or 0-2, respectively.
- Prior treatment: The PBS restriction did not include any conditions relating to previous treatment with endocrine therapy in early breast cancer (EBC), previous treatment with chemotherapy for advanced breast cancer. Patients were excluded from PALOMA-1 if they had prior treatment with (neo)adjuvant letrozole with disease recurrence  $\leq 12$  months, and from PALOMA-2 if they had prior neoadjuvant or adjuvant treatment with a NSAI with disease recurrence while on or within 12 months of completing treatment. Patients were excluded from both PALOMA-1 and PALOMA-2 if they had received chemotherapy or any other systemic therapy for advanced breast cancer.

2.4 The ESC considered that the PBS indication ‘Advanced Breast Cancer’ may be interpreted differently between clinicians, and that a clearer definition of the population for subsidised treatment would be appropriate. The ESC discussed that the eligibility criteria of the PALOMA-2 could be considered as a basis of this definition.

2.5 DUSC made the following comments on the proposed listing of palbociclib:

- Advanced cancer is not defined in the restriction and DUSC considered that it may be interpreted more broadly in practice. The PALOMA trials defined ‘advanced’ as metastatic (stage IV) and stage III inoperable. DUSC noted that other sources define ‘advanced’ differently, such as Cancer Australia which considers it is stage IV only and the NSW Cancer Registry defining it as Stage II onwards if there is lymph node involvement. DUSC noted that approximately 38% of women have locally advanced breast cancer at diagnosis<sup>1</sup>. DUSC considered under the broader definition of ‘advanced breast cancer’ there was the potential for use in early breast cancer, particularly where progression from Stage I to Stage II has occurred during endocrine therapy. DUSC considered that, to be consistent with current evidence, more appropriate wording for the restriction indication would be ‘Locally advanced inoperable and metastatic’.
- DUSC considered that the definition of initial endocrine-based therapy was unclear. In particular whether this excluded women who had a history of prior endocrine monotherapy or were currently receiving endocrine monotherapy at the time palbociclib is listed, or had undergone chemotherapy prior to endocrine therapy. DUSC noted that the TGA evaluator had recommended changing the proposed TGA indication to remove reference to first-line therapy. DUSC noted that there is no evidence for use in these populations as the PALOMA trials excluded patients who had received neoadjuvant or adjuvant treatment with a NSAI or who had received any prior anticancer therapy for advanced disease.

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<sup>1</sup> Walters, S., Maringe, C., Butler, J. et al. (2013). Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. *British Journal of Cancer* 108: 1195–1208.

- The PBS restriction specified that palbociclib should be used in combination with letrozole or anastrozole, whereas the proposed TGA indication specified that palbociclib should be used in combination with letrozole only. The Pre-Sub-Committee Response (PSCR, p1) provided expert opinions from oncologists, who indicated a preference to be able to use palbociclib in combination with anastrozole but stated that restriction to letrozole would not be problematic. DUSC considered that use of palbociclib in combination with anastrozole would be appropriate. DUSC noted the cost of combination therapy with either letrozole or anastrozole was similar as there were only marginal differences in the listed DPMQ for these drugs (\$36.15 vs. \$37.67 respectively as at February 2017).
  - DUSC noted that a further aromatase inhibitor, exemestane, was available on the PBS. While exemestane is indicated in second-line for post-menopausal women following prior adjuvant tamoxifen therapy, it has a broader PBS restriction (Item 8506Q) for hormone receptor positive breast cancer. DUSC commented that use of palbociclib in combination with exemestane was unlikely as this was not recommended.
  - There is a risk of treatment with palbociclib post-progression or as rechallenge due to the PBS restriction not specifying any conditions relating to ceasing treatment upon progression. DUSC considered that for palbociclib the risk of use beyond disease progression was minimal. DUSC further noted that in its PSCR (p1) the sponsor agreed with the inclusion of the stopping rule proposed by the PBAC Secretariat which may mitigate this risk: “A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug”.
  - Under the broader definition of hormone receptor positive (HR+) the restriction does not specify that patients must be oestrogen receptor positive (ER+). DUSC noted that patients may be HR+ if they are ER- and progesterone receptor positive (PgR+). The inclusion criteria in the PALOMA trials specified that patients were required to have an ER+ tumour, but no criteria were placed on their PgR status. DUSC noted that the TGA evaluator had recommended changing the proposed TGA indication to be in ER+ patients. DUSC noted that such a change will depend on the TGA’s evaluation of the full clinical study report for PALOMA-2. DUSC noted the advice in the PSCR (p1) that the evaluation outcomes for PALOMA-2 were expected to be available in the Delegate’s overview on 6 March 2017. Should ER-, PgR+ patients be included in the restriction, DUSC noted that they would represent only a very small number of patients.
- 2.6 In the pre-PBAC response, the sponsor agreed that ‘locally advanced inoperable or metastatic’ would be appropriate for the restriction indication, and agreed with the ESC and DUSC advice on other aspects of the PBS restriction.
- 2.7 The PSCR (p1) stated ‘The Sponsor did not initially request a ‘grandfather’ clause, but now understands that some patients are currently accessing palbociclib. Hence the Sponsor would like to request a ‘grandfather’ clause. The ESC noted that the number of patients currently accessing palbociclib was not provided in the PSCR, nor an indication if this patient access to the medicine aligns with the proposed restriction. The pre-PBAC response stated, ‘Approximately [REDACTED] patients would likely

be eligible for grandfathering, but it is not possible to estimate the number of patients currently purchasing palbociclib from international pharmacies, via the TGA SAS process’.

- 2.8 The requested basis for listing is a cost-utility analysis.

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

### **3 Background**

- 3.1 **TGA status at time of PBAC consideration:** At the time of the evaluation and the ESC meeting, the first round Clinical Evaluation Report was available. The PSCR (p1) provided an update stating that the full clinical study report for PALOMA-2 was under evaluation by the TGA and was expected to be addressed in the Delegate’s overview.

- 3.2 DUSC noted that the outcome of the TGA’s evaluation of the full clinical study report for PALOMA-2, anticipated in March 2017 (PSCR, p1), was required for further consideration of the submission. A supplementary Clinical Evaluation Report for Study A5481008 (PALOMA-2) was provided with the pre-PBAC response.

- 3.3 The PBAC noted that the 2<sup>nd</sup> Clinical Evaluation Report and TGA Delegate’s overview (for the April 2017 meeting of Advisory Committee on Medicines) were provided later than the pre-PBAC response. The PBAC noted that the Delegate’s Overview was not positive, with the TGA Delegate stating ‘I am not in a position to say, at this time, that the application for palbociclib should be approved for the first-line indication as follows:

*IBRANCE in combination with endocrine therapy is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with letrozole as initial endocrine-based therapy in postmenopausal women.’*

- 3.4 Palbociclib has not been considered by PBAC previously.

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

### **4 Clinical place for the proposed therapy**

- 4.1 Palbociclib is an oral, first in class, highly selective, reversible inhibitor of the cyclin-dependent kinases (CDK) 4 and 6. The recommended dose of palbociclib is: 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days

- 4.2 The submission proposed palbociclib be used in combination with an NSAID as initial endocrine treatment for postmenopausal women with HR+, HER2- ABC.

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

## 5 Comparator

- 5.1 The submission nominated NSAI alone (letrozole or anastrozole) as the main comparator. The ESC noted that the clinical management algorithm presented in the submission proposed that palbociclib may also replace first line treatment options of tamoxifen and exemestane. NSAI is recommended in both Australian and USA guidelines over tamoxifen in the majority of women, and that choice of first line agent relies on the treatment efficacy and toxicity profile, and patient/physician preference. The ESC considered that in clinical practice, NSAI would be generally used ahead of tamoxifen and exemestane, and so the choice of NSAI as the nominated comparator was reasonable.

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

## 6 Consideration of the evidence

### **Sponsor hearing**

- 6.1 The sponsor requested a hearing for this item. The clinician summarised some of the clinical evidence provided in the submission and their clinical experience with patients receiving the medicine. The PBAC found details of the clinician's use of palbociclib in clinical practice informative.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from individuals (6), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals described a range of benefits of treatment with palbociclib including improved quality of life, manageable side effects, slowed disease progression, delayed time to chemotherapy, but also noted its very high financial cost. The Centre for Community-Driven Research said that patients with advanced breast cancer are calling for more choice in their treatment options. The Breast Cancer Network Australia advocated for Australian patients to have access to the same treatments as people in other parts of the world, and stated that palbociclib has many benefits, including the convenience of oral therapy (particularly in rural areas), lower toxicity profile compared to chemotherapy, and delaying the onset of chemotherapy.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the palbociclib submission, on the basis of PFS benefit. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for palbociclib in combination with a NSAI, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>2</sup>, based on a comparison with NSAI alone.

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<sup>2</sup> Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26:1547-73, 2015.

**Clinical trials**

6.4 The submission was based on two head-to-head RCTs comparing palbociclib + letrozole to letrozole alone:

- PALOMA-1: an open-label, multicentre, phase II RCT for first line treatment of ER+, HER2- ABC in postmenopausal women.
- PALOMA-2: a double-blind, randomised, multicentre, placebo-controlled, parallel-group, phase III trial for first line treatment of ER+, HER2- ABC in postmenopausal women.

6.5 Details of the trials presented in the submission are provided in the table below.

**Table 1: Trials and associated reports presented in the submission**

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
PALOMA-1 A5481003 [NCT00721409]	Clinical Study Report A5481003 (30 July 2015). Phase 1/2, Open-Label, Randomised Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole Plus PD 0332991 (Oral CDK 4/6 Inhibitor) and Letrozole Single Agent for the First-Line Treatment of ER-Positive, HER2-Negative Advanced Breast Cancer in Postmenopausal Women. Finn, RS Crown, JP Lang, I et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Finn, RS Crown, JP, Ettl J et al. Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomised pivotal trial PALOMA-1/TRIO-18. Bell, T Crown, JP Lang, I Bhattacharyya, H Zanotti, G Randolph, S Kim, S Huang, X Bartlett, CH Finn, R Slamon, D. Impact of adding palbociclib to letrozole on pain severity and pain interference with various activities of daily life in patients with ER+, HER2- metastatic breast cancer as first line treatment.	30 July 2015.  The Lancet Oncology 2015; 16:25-35.  Breast Cancer Research (2016) 18:67.  Cancer research (2015) 75:9 SUPPL.1
PALOMA-2 A5481008 [NCT01740427]	Clinical Study Report A5481008 (11 August 2016). A Randomised, Multicenter, Double-Blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women With ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment for Advanced Disease. Finn, RS Martin, M Hope, S et al. PALOMA-2: Primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2- advanced breast cancer (ABC).	11 August 2016  J Clin Oncol 34, 2016 (suppl; abstract 507).

Source: Table B.2.3, p29 of the submission.

6.6 The key features of the direct randomised trials are summarised in the table below.

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Palbociclib plus letrozole vs. letrozole</b>						
PALOMA-1	165	R, OL P+L: 13.8 mths & 14.07 mths L: 7.6 mths	High	Treatment naïve ER+/HER2- ABC	Primary: investigator assessed PFS Secondary: BICR PFS, OS; 1, 2, & 3- y survival; TTP; OR; CBR; DOR; AE; PROs	PFS and OS used in base case
PALOMA-2	666	R, DB P+L: 19.8 mths L: 13.6 mths	Low	Treatment naïve ER+/HER2- ABC	Primary: investigator assessed PFS Secondary: BICR PFS, OS; OR; DOR; DC; CBR; PROs; AE	PFS and PROs used in sensitivity analysis

ABC=Advanced breast cancer; BICR= Blinded Independent Central Review; DB=double blind; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; TTP=Time to progression, OR=Objective response; CBR=Clinical benefit rate; DOR=Duration of response; AE=Adverse Events; PROs=Patient-reported outcomes. Source: compiled during the evaluation

6.7 Tumour response, investigator assessed PFS and patient reported outcomes are potentially subject to bias in PALOMA-1 because of the open label design of the trial. The ESC noted that while reported outcomes of PALOMA-1 are more mature than PALOMA-2, PALOMA-1:

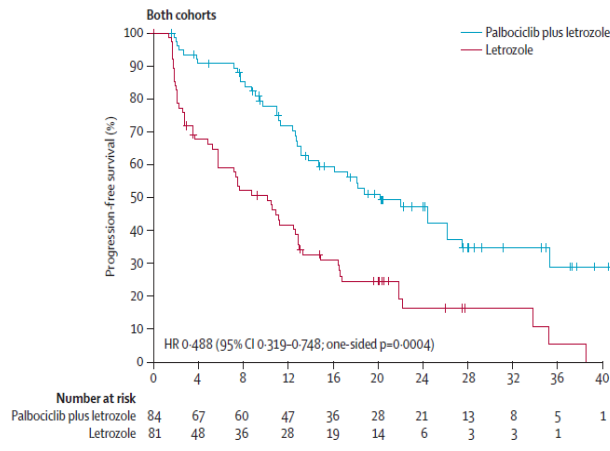
- was an adaptive, open label Phase II exploratory trial with power of 80% to demonstrate PFS at alpha of 0.1; not powered or designed to demonstrate OS;
- had changes to the trial protocol as data was collected;
- had changes to the eligibility criteria during the course of the trial based on biomarker status;
- has a higher risk of bias than PALOMA-2; and
- had a smaller number of patients than PALOMA-2.

### **Comparative effectiveness**

6.8 The submission relied on PFS and OS for its clinical claim. OS results were not available for PALOMA-2.

6.9 Figures 1 to 4 demonstrate the difference between the investigator assessed and the Blinded Independent Central Review (BICR) assessed PFS.

Figure 1: PALOMA-1 Kaplan-Meier Plot of PFS – Investigator Assessment (ITT Population)



Source: Figure B.6.1 p64 and Figure B.6.2 p66 of the submission

Figure 2: PALOMA-1 Kaplan-Meier Plot of PFS – BICR (ITT Population)

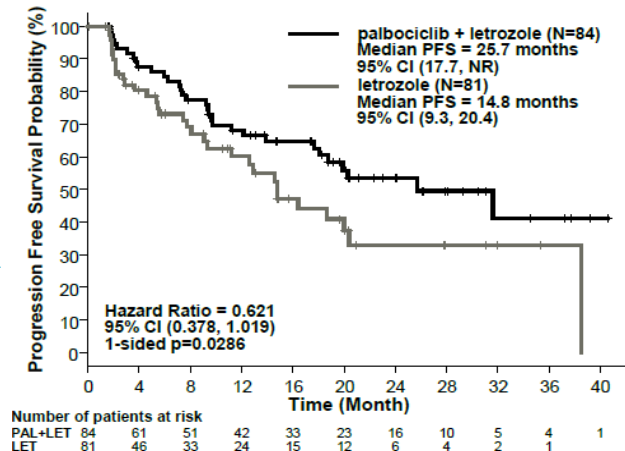
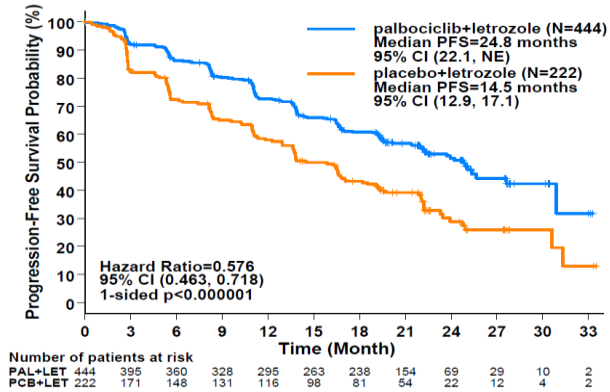


Figure 3: PALOMA-2 Kaplan-Meier Plot of PFS – Investigator Assessment (ITT Population)



Source: Figure B.6.7 p79 and Figure B.6.10 p86 of the submission

Figure 4: PALOMA-2 Kaplan-Meier Plot of PFS – BICR (ITT Population)

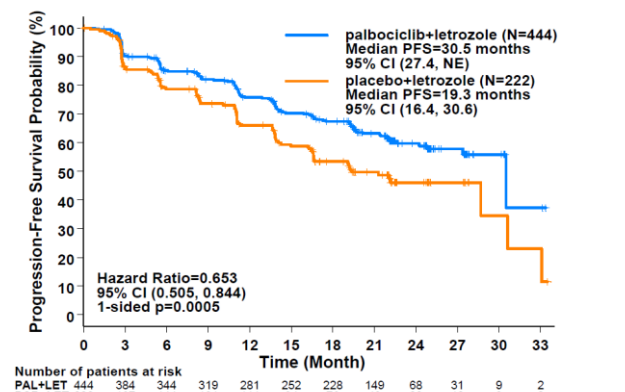
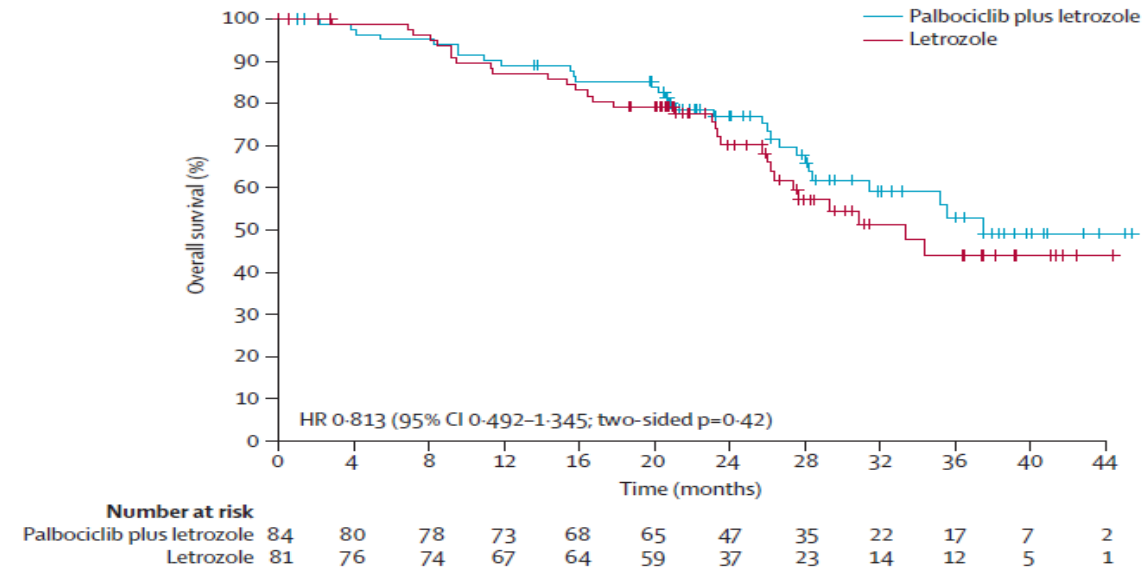


Figure 5: PALOMA-1 Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population)



Source: Figure B.6.4 p71 of the submission

Table 3: PFS and OS results of across the direct randomised trials

Trial ID	P + L n with event/N (%)	L n with event/N (%)	P + L Median months (95% CI)	L Median months (95% CI)	Diff.	HR (95% CI)
<b>PFS</b>						
<b>PALOMA-1</b>						
Investigator	41/84 (48.8)	59/81 (72.8)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)	10.0	HR 0.488 <sup>a</sup> (0.319, 0.748)
BICR	31/84 (36.9)	33/81 (40.7)	25.7 (17.7, NR)	14.8 (9.3, 20.4)	10.9	1-sided p-value 0.0004 <sup>b</sup> HR 0.621 <sup>a</sup> (0.378, 1.019) 1-sided p-value <sup>b</sup> 0.0286
<b>PALOMA-2</b>						
Investigator	194/444 (43.7)	137/222 (61.7)	24.8 (22.1, NR)	14.5 (12.9, 17.1)	10.3	HR 0.576 <sup>a</sup> (0.463, 0.718)
BICR	152/444 (34.2)	96/222 (42.3)	30.5 (27.4, NR)	19.3 (16.4, 30.6)	11.2	2-sided p-value <0.000001 HR 0.653 <sup>a</sup> (0.505, 0.844) 2-sided p-value 0.000532
<b>Overall survival</b>						
<b>PALOMA-1</b>						
	30/84 (35.7)	31/81 (38.3)	37.5 (28.4, NR)	33.3 (26.4, NR)	4.2	HR 0.813 <sup>a</sup> (0.492, 1.345) 1-sided p-value 0.2105 <sup>b</sup>

BICR= Blinded Independent Central Review; P = palbociclib, L = letrozole; NR=not reported.

<sup>a</sup> Assuming proportional hazards, HR = Hazard Ratio. A hazard ratio < 1 indicates a reduction in hazard rate in favour of Palbociclib + letrozole.

<sup>b</sup> 1-sided p-value from the log-rank test stratified by Part.

Source: Table B.6.1 p65, B.6.2 p67, B.6.10 p80, B.6.12 p85 and Table B.6.4 p70 of the submission and calculated during the evaluation.

- 6.10 The median difference of PFS in PALOMA-2 was 11.2 months by BICR compared to 10.3 months when investigator assessed. This difference is based on a measure at one point of time (median). The PBAC noted in both the PALOMA-1 and PALOMA-2 trials that the difference in hazard ratios (table 3), and separation of Kaplan-Meier curves between the treatment groups (figures 1 to 4), which show the benefit over the trial follow-up, suggested that the investigator assessed results were over-estimated compared to the BICR results. The PBAC noted no statistically significant difference in overall survival between treatment groups in PALOMA-1 based on a data cut-off from November 2013, with more recent data not available. The PBAC noted that survival data for PALOMA-2 would not be available until 2020,

### Comparative harms

- 6.11 In PALOMA-1 and PALOMA-2, substantially more patients treated with palbociclib + letrozole were reported to have AEs compared with those treated with letrozole alone. The key differences between the treatment arms were:
- More patients treated with palbociclib + letrozole had grade  $\geq 3$  AEs (PALOMA-1: 78.3% vs. 20.8%, PALOMA-2: 79.8% vs. 27.0%). In PALOMA-1, there were 3 cases of pulmonary embolism (3.6%) in the palbociclib + letrozole arm, compared to nil cases in the letrozole arm. Pulmonary embolism (1.6%) and deep vein thrombosis (0.9%) were reported in the combination arm of PALOMA-2, but the submission considered that these were not treatment-related. The FDA label<sup>3</sup> warns that healthcare providers should check white blood cell counts before and during treatment due to neutropenia and that the drug may cause pulmonary embolism. The ESC noted patients with pulmonary embolism would require lifetime treatment with anti-coagulants.
  - More patients treated with palbociclib + letrozole temporarily discontinued treatment due to AEs (PALOMA1: **P+L**: P 62.7%, L 14.5% vs. **L**: P 1.3%, L 3.9%, PALOMA-2: **P+L**: P 74.8%, L NR vs. **L**: P 9.9%, L NR).
  - More patients treated with palbociclib + letrozole discontinued treatment (PALOMA-1: 14.5% vs. 2.6%, PALOMA-2: **P+L**: P 9.2% L 6.1% vs. **L**: P 5.4% L 5.0%) or had a dose reduction (PALOMA-1: 38.6% vs. NA, PALOMA-2: 36.0% vs. 1.4%).
  - In patients treated with palbociclib + letrozole the most common AEs included neutropenia (PALOMA-1: 74.7%, PALOMA-2: 79.5%), leukopenia (PALOMA-1: 43.4%, PALOMA-2: 39.0%), fatigue (PALOMA-1: 41.0%, PALOMA-2: 37.4%) and infections (PALOMA-1: NR, PALOMA-2: 59.7%). The ESC noted a higher rate of infections in patients treated with palbociclib + letrozole (PALOMA-2: 59.7% vs 42.3%), but the nature and severity of the infections were unclear.
  - In patients treated with palbociclib + letrozole the most common grade 3 or 4 AEs included neutropenia (grade 4) (PALOMA-1: 6.0%, PALOMA-2: 10.4%), neutropenia (grade 3) (PALOMA-1: 48.2%, PALOMA-2: 56.1%) and leukopenia (grade 3) (PALOMA-1: 19.3%, PALOMA-2: 24.1%).
- 6.12 The submission claimed that the addition of palbociclib to letrozole maintained health-related quality of life. The submission argued that there were no statistically significant differences between the treatment arms in PALOMA-2. The PALOMA-1 trial was not powered to detect changes in patient reported outcomes (PROs). The PBAC noted that there was no evidence provided to suggest that palbociclib improved quality of life.

### Benefits/harms

- 6.13 A summary of the comparative benefits and harms for palbociclib + letrozole versus letrozole alone is presented in the table below.

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<sup>3</sup> FDA 02/19/2016. Ibrance (palbociclib), Labels for NDA 207103  
<http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varAppNo=207103>

**Table 4: Summary of comparative benefits and harms for palbociclib**

<b>Benefits</b>						
<b>PFS (Investigator assessed): PALOMA-1</b>						
	<b>P + L</b>	<b>L</b>	<b>Absolute Difference</b>		<b>HR (95% CI)</b>	
Progressed	41/84 (48.8%)	59/81 (72.8%)	-		0.488 (0.319, 0.748)	
Median (mths)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)	10.0			
<b>PFS (BICR): PALOMA-1</b>						
Progressed	31/84 (36.9%)	33/81 (40.7%)	-		0.621 (0.378, 1.019)	
Median (mths)	25.7	14.8	10.9			
<b>PFS (Investigator assessed): PALOMA-2</b>						
Progressed	194/444 (43.7%)	137/222 (61.7%)	-		0.576 (0.463, 0.718)	
Median (mths)	24.8 (22.1, NE)	14.5 (12.9, 17.1)	10.3			
<b>PFS (BICR): PALOMA-2</b>						
Progressed	152/444 (34.2%)	96/222 (42.3%)	-		0.653 (0.505, 0.844)	
Median (mths)	30.5	19.3	11.2			
<b>OS: PALOMA-1</b>						
Died	30/84 (35.7%)	31/81 (38.3%)	-		0.813 (0.492 – 1.345)	
Median (mths)	37.5 (28.4, NR)	33.3 (26.4, NR)	4.2			
<b>Harms</b>						
	<b>P + L</b>	<b>L</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients*</b>		<b>RD (95% CI)</b>
				<b>P + L</b>	<b>L</b>	
<b>Grade&gt;3 adverse events</b>						
PALOMA-1	65/83	16/77	3.769 (2.402, 5.914)	78.3	20.8	57.5% (44.9%, 70.2%)
PALOMA-2	354/444	60/222	2.950 (2.365, 3.680)	79.8	27.0	52.7% (45.8%, 59.6%)
<b>Neutropenia</b>						
PALOMA-1	62/83	NR/81	122.0 (7.7, 1940.0)*	74.7	NR	74.7% (65.3%, 84.1%)
PALOMA-2	353/444	14/222	12.607 (7.576, 20.979)	79.5	6.3	73.2% (68.3%, 78.1%)
<b>Febrile neutropenia</b>						
PALOMA-1	0/83	0/81	-	0	0	-
PALOMA-2	11/444	0/222	11.5 (0.7, 194.7)*	2.6	0	2.5% (1.0%, 3.9%)
<b>Leukopenia</b>						
PALOMA-1	36/83	NR/81	71.262 (4.447, 1141.964)*	43.4	NR	43.4% (32.7%, 54.0%)
PALOMA-2	173/444	5/222	17.3 (7.216, 41.475)	39.0	2.3	36.7% (31.8%, 41.6%)
<b>Fatigue</b>						
PALOMA-1	38/83	18/77	1.75 (1.08, 2.83)	41.0	23.4	17.6% (3.1%, 31.0%)
PALOMA-2	166/444	61/222	1.36 (1.06, 1.74)	37.4	27.5	9.9% (2.3%, 17.0%)

Abbreviations: P = palbociclib, L = letrozole; PBO = placebo; RD = risk difference; RR = risk ratio; HR=Hazard Ratio; PFS=Progression-free Survival; OS=Overall Survival.

Source: Compiled during the evaluation and Table B.6.4 p70, Table B.6.1 p65, B.6.2 p67, B.6.10 p80, B.6.12 p85 Table B.6.28, Table B.6.34, p119-120 of the submission and Table 14.3.2.1.1.a and Table 14.3.2.1.1.b of PALOMA-1 CSR. \*adding 0.5 cases of neutropenia to each treatment arm.

- 6.14 On the basis of direct evidence presented by the submission, there would be approximately a 10 month increase in median PFS in patients treated with palbociclib plus letrozole in comparison with letrozole alone. A statistically significant increase in overall survival was not demonstrated in the trials. For every 100 patients treated with palbociclib plus letrozole in comparison with letrozole alone, over a median follow-up of around 23 months:
- Approximately 54 additional patients would experience a grade  $\geq 3$  adverse event;
  - Approximately 74 additional patients would experience neutropenia;
  - Approximately 2 additional patients would experience febrile neutropenia;
  - Approximately 38 additional patients would experience leukopenia;
  - Approximately 12 additional patients would experience fatigue; and
  - The increased risk of pulmonary embolism was small but observed in both clinical trials.

### **Clinical claim**

- 6.15 The submission described palbociclib plus letrozole as having: “Superior comparative effectiveness to letrozole (or anastrozole) as the main comparator and a slightly worse but manageable safety profile”. The evaluation appraised that the claim was not adequately supported. The ESC noted the following issues:
- PALOMA-1 and PALOMA-2 compared palbociclib + letrozole to letrozole alone. The effect of palbociclib + anastrozole compared to anastrozole alone in terms of efficacy and safety was not estimated, though the ESC considered on balance in clinical practice, it would be reasonable to expect that letrozole or anastrozole would provide a similar benefit in combination with palbociclib.
  - The OS results from PALOMA-1 were immature and the difference in OS was not statistically significant. OS results from PALOMA-2 are expected in 2020.
  - PALOMA-1 was an open-label study, and as such the investigator assessed tumour response and PFS results, and patient reported outcomes, may be biased in favour of palbociclib. In addition, PALOMA-1 was a Phase II exploratory trial, had changes to the trial protocol as data were collected, has a higher risk of bias than PALOMA-2, and had a smaller number of patients than PALOMA-2.
  - Palbociclib plus letrozole is inferior in terms of safety compared to letrozole alone due to increased incidence of neutropenia, leukopenia, fatigue and infections. Also, a higher incidence of grade 3-4 adverse events were observed with palbociclib plus letrozole.
  - The claim that palbociclib plus letrozole vs. letrozole alone maintained quality of life in both studies is not adequately supported. PALOMA-1 was not powered to detect changes in PROs.
  - The complete response rates in both trials were low and not different between the arms, for example in PALOMA-2, the complete response was 2.3% in both arms. The submission and the pre-PBAC response stated the mechanism of cell cycle inhibition by palbociclib is not cytotoxic but cytostatic, it arrests cell division which results in a high level of stable disease and inhibition of further cancer growth. Low complete response rates are therefore expected.
- 6.16 According to the PSCR (p. 2), the neutropenia associated with use of palbociclib differs in intensity, duration and frequency compared to chemotherapy-induced neutropenia, and can be effectively managed by dose interruption, delay or dose

reduction. The ESC noted that palbociclib had a direct effect on a patient's neutrophil count. While in many patients, there was transient neutropenia, which was not clinically significant, the ESC noted that neutropenia was prolonged in a significant number of patients, which may have the effect of delaying future treatments. Although the PSCR also noted that febrile neutropenia is rare in patients receiving palbociclib, the ESC disagreed and considered that the trials were not powered to detect febrile neutropenia, and the risk may be higher in clinical practise as monitoring is less stringent. The pre-PBAC response reiterated that adverse events would be managed by clinicians in consultation with the product information, as well as stating permanent discontinuation associated with an adverse reaction occurred in 4.7% of patients receiving palbociclib in PALOMA-1 and PALOMA-2, and in 2% of patients in the comparator arms. It was further noted to date, over 50,000 patients have been treated with palbociclib and the most recent Periodic Safety Update Report (3 Feb. 2016 - 2 Aug. 2016) confirms the known safety profile of palbociclib and did not present any new significant safety information with palbociclib.

- 6.17 The PSCR (p1) argued the unsurpassed median progression-free survival (PFS) of 24.9 months [stated in this document as 24.8 months, with a comparative median PFS of 10.3 months], coupled with the high unmet clinical need for patients with advanced HR+ HER2- breast cancer (a patient population who have had no new treatments for 18 years), makes a compelling case for allowing patients access to this treatment. The ESC agreed that palbociclib provided a significant improvement in PFS, but considered that OS improvement has not yet been demonstrated. The ESC noted that the numerical but non-significant differences in OS were applied in the economic model.

### **Economic analysis**

- 6.18 The submission presented a stepped economic evaluation, based on PALOMA-1 and implementing a modelled evaluation. The types of economic evaluation presented were a cost-utility analysis and a cost-effectiveness analysis.

**Table 5: Summary of model structure and rationale**

<b>Component</b>	<b>Summary</b>
Type of analysis	Cost-effectiveness analysis and cost-utility analysis.
Outcomes	Time in pre-progression health state, LYG and QALYs.
Time horizon	130 cycles (9.97 years) in the model base case versus a maximum of 44 months in the PALOMA-1 trial. Sensitivity analyses included a time horizon of 44 months.
Methods used to generate results	A Markov model.
Health states	1) alive pre-progression 2) alive post-progression 3) death
Cycle length	28 days
Half-cycle correction applied	Yes
Transition probabilities	Kaplan-Meier estimates for PFS and OS in PALOMA-1 until cycle 39, extrapolated using a log-logistic function until cycle 130.
Discount rate	5% for costs and outcomes

Source: compiled during the evaluation

- 6.19 The key drivers of the model are provided in the table below.

**Table 6: Key drivers of the model**

Description	Method/Value	Impact
Time horizon	10 years; extrapolated from 44 months.	High, favours palbociclib
Source of PFS	Investigator assessed PFS from PALOMA-1 (rather than PALOMA-2).	High, favours palbociclib
	Investigator assessed PFS (rather than BICR assessed PFS).	Unknown, favours palbociclib
Total cost of palbociclib	Patients assumed to end treatment when reaching median number of cycles from the trial	High, favours palbociclib
Total cost of letrozole	Costs assumed to cancel out between palbociclib + letrozole and letrozole arms despite different durations of therapy	Moderate, favours palbociclib. The pre-PBAC response argued that inclusion of the addition costs of letrozole increased the ICER from \$ [REDACTED] /QALY to \$ [REDACTED] /QALY. A minimal impact.
OS gain	OS from PALOMA-1 (not statistically significant).	High, favours palbociclib
Disease costs post-progression	\$ [REDACTED] per annum. Error in calculation. Using the method defined in the submission, should be \$ [REDACTED] per annum. The PSCR presented an alternative source, with the value of \$ [REDACTED] (see discussion below).	High, favours palbociclib
Adverse events	Hospitalisation costs for treatment related adverse events not included.	Unknown, likely favours palbociclib
Extrapolation	Application of the log-logistic function to extrapolate PFS and OS (rather than a Weibull function for OS). The approach effectively assumes that the treatment effect persists for the model duration.	Moderate, favours palbociclib

Source: compiled during the evaluation

- 6.20 Figure 6 and Figure 7 demonstrate the impact of extrapolating the PFS and OS Kaplan-Meier curves, for the different extrapolation functions considered. The ESC noted that the model is sensitive to the function used to extrapolate the trial data and the period over which it is extrapolated.

Figure 6: Observed PFS and extrapolated PFS from PALOMA-1 (submission uses log-logistic, yellow)  
[Figure redacted]

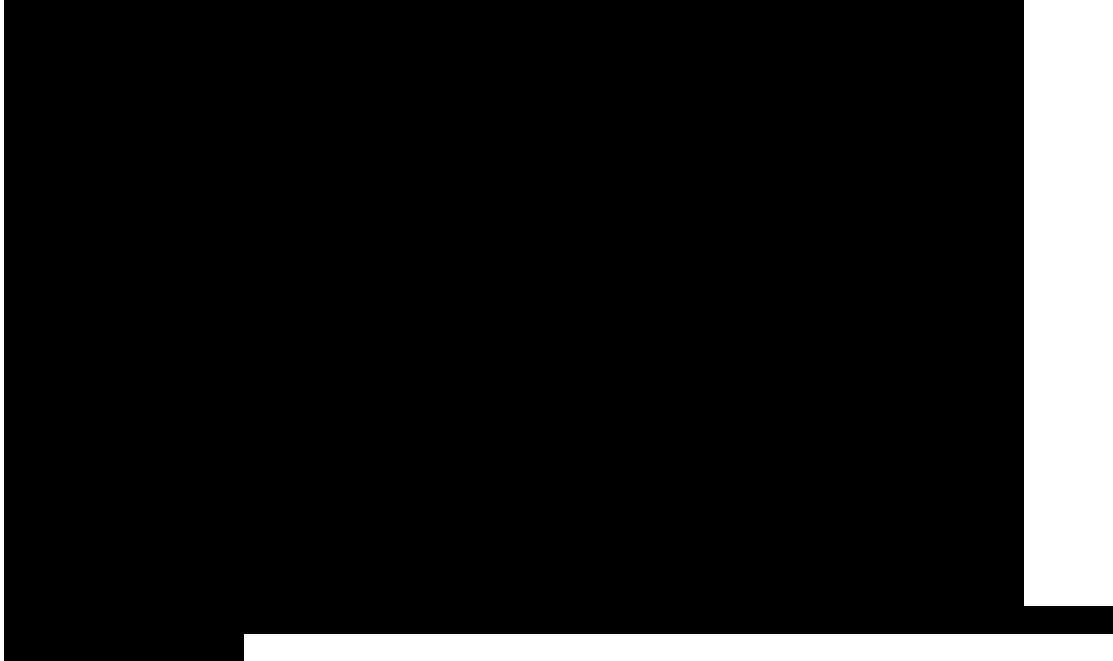


Figure 7: Observed OS and extrapolated OS from PALOMA-1 (submission uses log-logistic, yellow)  
[Figure redacted]



- 6.21 The table below presents the results of the stepped economic evaluation.
- 6.22 The ICER in terms of the incremental cost per QALY gained is lower than the incremental cost per life year gained because the gain in OS (median = 4.2 months in PALOMA-1) is substantially shorter than the gain in PFS (median = 10.0 months in PALOMA-1, investigator assessed).

Table 7: Results of the stepped economic evaluation

Step and component	Palbociclib group (palbociclib + letrozole)	Usual care group (letrozole alone)	Increment
<b>Step 0: trial-based costs and outcomes (time horizon = 39 cycles)</b>			
Costs	\$ [redacted] <sup>a</sup>	\$ [redacted] <sup>a</sup>	\$ [redacted] <sup>a</sup>
Years of life lived	2.279 <sup>a</sup>	2.180 <sup>a</sup>	0.100 <sup>a</sup>
<b>Incremental cost/extra years of life gained<sup>a</sup></b>			\$ [redacted] <sup>a</sup>
<b>Step 1: modelled evaluation (time horizon = 10 years or 130 cycles)</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Years of life lived	3.584	3.197	0.387
<b>Incremental cost/extra years of life gained</b>			\$ [redacted]
<b>Step 2: modelled evaluation (time horizon = 10 years, incorporating utilities)</b>			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
QALYs	2.420	1.897	0.523
<b>Incremental cost/extra QALY gained</b>			\$ [redacted]
<b>Disease costs post progression = \$ [redacted] (see discussion below).<sup>a</sup></b>			\$ [redacted] <sup>a</sup>
<b>Disease costs post progression based on Verry et al (2012), PSCR, p4</b>			\$ [redacted]

Source: D.5.2 and D.5.3, p205 of the submission

<sup>a</sup> Added during the evaluation

The redacted table shows ICERs in the range of \$45,000/QALY - \$75,000/QALY to more than \$200,000/QALY.

- 6.23 The submission assumed that the palbociclib treatment duration was 20.2 months, equivalent to 22 cycles, as per the median PFS among patients randomised to palbociclib plus letrozole in PALOMA-1. This is likely to under-estimate the cost of providing palbociclib for two reasons: 1) the distribution of use is likely to be skewed, so the median is likely to lie below the mean; and 2) the model assumes no usage beyond 22 cycles, which is not reflected in the trial data. The ESC noted that in the economic model, the undiscounted cost of palbociclib was \$ [redacted], while the drug cost/patient/course (see below) was calculated as \$ [redacted]. The ESC considered using the time to discontinuation from the PALOMA-1 trial may be an alternative method to address this issue. The pre-PBAC response reiterated that cost of \$ [redacted] in the model was the 'average' cost for the entire palbociclib group, some of whom would have progressed or died within the model time horizon, and hence ceased treatment. The PBAC agreed with the ESC that [redacted] the costs of palbociclib were underestimated.
- 6.24 The submission did not provide an Excel spreadsheet that illustrates how the resource utilisation study was combined with the unit costs to estimate the pre- and post-progression, and one-off costs applied in the economic model, which hindered the evaluation. During the evaluation it was noted that a copying error resulted in the submission estimating post-progression costs to be \$ [redacted], rather than \$ [redacted]. Using the lower post-progression cost increased the ICER from \$45,000/QALY – \$75,000/QALY to \$75,000/QALY – \$105,000/QALY.
- 6.25 The PSCR (p2) acknowledged the error relating to the post-progression disease costs. The PSCR stated post-progression disease costs derived from the survey were an obvious underestimate, as they were lower than the pre-progression costs (\$ [redacted] vs \$ [redacted]). The PSCR carried out a literature search and identified new data sources for resource use, including Verry et al (2012) British Journal of Cancer. The

PSCR re-estimated annual pre-progression costs, annual post-progression costs, and once-off cost of death costs based on this publication, shown in the table below.

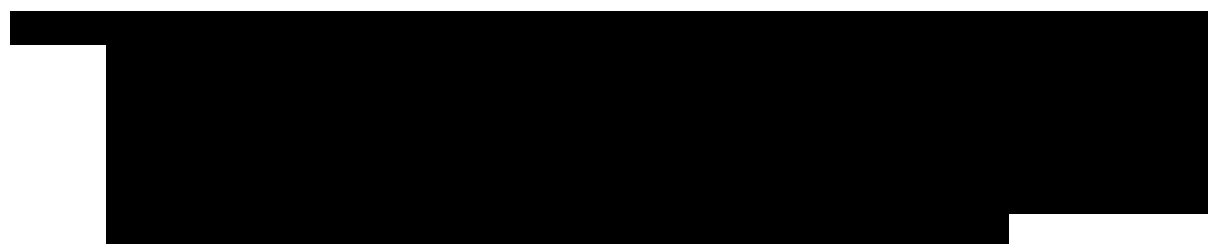
**Table 8: Comparison of costs**

Unit costs	Resource utilisation survey in submission	Verry et al (2012) in PSCR
Annual pre-progression costs	\$ [REDACTED]	\$5340
Annual post-progression costs	\$ [REDACTED] (submission) \$ [REDACTED] (corrected during evaluation).	\$24,340
End of life and death (one-off)	\$ [REDACTED]	\$29,615.97
ICER	\$ [REDACTED]/QALY (submission)	\$ [REDACTED]/QALY

Source: Table 2 of the PSCR.

- 6.26 The ESC was uncertain of which source of cost was reasonable to apply to the economic model. The costs presented in PSCR may overstate the cost of post-progression, while the corrected error may understate these costs. In the submission, the disease-related costs were estimated from a health services utilisation survey conducted between 13 November and 22 December 2015. The Verry et al (2012) publication:
- did not report the year of the analysis, however drug costs and medical services were based on the PBS and MBS in 2011, while hospitalisation costs were based on the Australian Refined Diagnosis Related Groups (AR-DRG) Version 5.1 published in 2008.
  - did not report which drugs were used to estimate the costs of third-generation and fourth-generation chemotherapy. The cost of many chemotherapies used to treat breast cancer, such as docetaxel, vinorelbine, gemcitabine and capecitabine have declined significantly in recent years.
  - used a publication from 1991 as the source of end of life costs.
- 6.27 The pre-PBAC response state ‘the post-progression cost from Verry et al (2012) provide a contemporary, robust Australian estimate that is appropriate to inform the economic model’. The PBAC disagreed and considered reliable up to date estimates of the pre and post-progression costs were not provided in the submission.
- 6.28 The use of PFS from PALOMA-1 in the base case, rather than PALOMA-2, favours palbociclib; if PFS from PALOMA-2 were used, the cost/QALY increased to \$105,000/QALY – \$200,000/QALY relative to the submission base case of \$45,000/QALY – \$75,000/QALY. The PSCR (p. 2) stated that PFS from PALOMA-1 was used to ensure internal validity, as OS data were also available from PALOMA-1. Further, the duration of follow-up for PALOMA-1 PFS was longer than that of PALOMA-2 PFS, requiring less extrapolation of the results. The ESC and PBAC noted that the use of PFS from PALOMA-1, and use of investigator assessed rather than blinded centrally assessed PFS, both favours palbociclib. The PBAC considered the model should be informed by the blinded centrally assessed PFS results for PALOMA-2.
- 6.29 The submission presented several univariate sensitivity analyses. During the evaluation additional sensitivity analyses were conducted to assess the impact of various assumptions and correct calculations of health resource costs. The results of the sensitivity analyses indicate that the model is most sensitive to:

- The time horizon of the model. The increase in OS in the PALOMA-1 trial was not statistically significant ( $p=0.813$ ) and therefore not clearly demonstrated. This issue was amplified by extrapolating the survival data out to 10 years from only 44 months of follow-up. The mean increase in OS at cycle 39 was [REDACTED], which increased to [REDACTED] at the end of the model (undiscounted). In general, previous economic models considered by the PBAC applied a shorter time horizon when the OS gain was not statistically significant. A shorter time horizon may be appropriate. Application of a shorter time horizon increased the ICER. The pre-PBAC response stated that the mean increase in OS of [REDACTED] was less than the 10-month PFS gain observed in PALOMA-1 and PALOMA-2. The economic model was informed by the numerical difference in OS from PALOMA-1 and did not attribute the 10-month gain in PFS to OS.
- The use of PFS from PALOMA-1 in the base case, rather than from PALOMA-2, favours palbociclib.
- The assumption that palbociclib increases OS (which was not statistically significant in PALOMA-1). The current approach favours palbociclib.
- The application of the log-logistic function to extrapolate OS, rather than the Weibull function. The Weibull function had a slightly lower AIC and BIC and the choice of extrapolation function had a moderate impact on the ICER. The current approach favours palbociclib.



- 6.30 The impact of excluding hospitalisation costs for treatment related adverse events is unknown due to the lack of a formal sensitivity analysis conducted by the submission, however the current approach is likely to favour palbociclib given the higher rate of adverse events. The PSCR (p4) provided a sensitivity analysis including the cost of hospitalisations due to adverse events. It was estimated that the marginal cost of serious adverse events (SAEs) for palbociclib was \$[REDACTED] per person. This amount was added as a 'one-off' cost to the cost of palbociclib. The ICER increased from \$45,000/QALY – \$75,000/QALY to \$45,000/QALY – \$75,000/QALY. The ESC noted that this does not fully address the costs of adverse events, as it does not consider:
- the less expensive, but more frequent, lower level adverse events; or
  - events such as febrile neutropenia, which would result in hospitalisation, may be underestimated, noting that approximately 2% febrile neutropenia was reported in PALOMA-2.
- 6.31 The ESC noted that a fuller range of adverse event costs were not incorporated into the model. In addition, there is more intensive monitoring of patients compared to those treated with current treatments. For example, for the first two cycles (of 28 days), blood testing would be carried out at baseline/day 0 and then day 14 and day 21, plus increased clinic visits and reviews. The impact of including monitoring and adverse events would increase the ICER, by an unknown amount. In addition, the ESC noted that, while there was a worse adverse event profile in the palbociclib arm of PALOMA-2, there was no decrement in the quality of life (QOL) reporting (EQ-5D

scores). The ESC was uncertain if this was due to a lack of sensitivity in the QOL instrument or if, perhaps, the slowing of disease counteracts the patient’s adverse events.

**Table 9: Results of key univariate sensitivity analyses**

Univariate analyses	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness (\$/QALY)
Base case (in submission)	\$ [redacted]	0.523	\$ [redacted]
Time horizon = 44 months (PALOMA-1 duration)	\$ [redacted]	0.275	Corrected during evaluation = \$ [redacted]
PALOMA-2 KM data (PFS) alone	\$ [redacted]	0.404	\$ [redacted]
OS for palbociclib + letrozole = letrozole alone in PALOMA-1	\$ [redacted]	0.280	\$ [redacted]
Weibull extrapolation OS only - Cycles 40+	\$ [redacted]	0.475	\$ [redacted]

Source: D.6.1, p206 of the submission and compiled during the evaluation using Palbociclib Section D – Nov 2016.xlsx

The redacted table shows ICERs in the ranges \$45,000/QALY - \$75,000/QALY to \$105,000/QALY - \$200,000/QALY.

- 6.32 The PSCR (p4-5) presented sensitivity analyses which extrapolated survival curves for PFS and OS from earlier time points. From the PSCR base case (\$45,000/QALY – \$75,000/QALY, 39 cycles), the ICER varied between \$45,000/QALY – \$75,000/QALY (0 cycles) to \$45,000/QALY – \$75,000/QALY (35 cycles). The PBAC noted the extrapolations have been inappropriately undertaken from the ends of the Kaplan-Meier curves which are informed by a very small number of patients, and this favoured palbociclib.

**Figure 8: Sensitivity analysis exploring the impact of extrapolation of survival curves from earlier time-points [Figure redacted]**



- 6.33 Overall, the ESC noted the base case assumptions presented in the PSCR resulting in an ICER of \$45,000/QALY – \$75,000/QALY, but considered that this base case is likely an underestimate. The ESC, given the issues raised above, was unable to redefine a plausible base case for the PBAC’s consideration. The pre-PBAC response argued that the PSCR base case provided a plausible estimate of the cost-effectiveness of palbociclib. The PBAC considered the ICERs presented in the submission and the sponsor’s responses to be unreliable, and substantially underestimated.

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

- 6.34 Assuming a cost of \$ [REDACTED] per pack, one pack is used per 28 days, no dose reduction, and the patient is treated for 24.8 months (and thus receive 27 packs) (i.e. until progression). The ESC noted that this assumption was based on the median value, and the average cost may be higher. The proposed PBS listing did not restrict use following progression on treatment. Patients may use palbociclib past progression. The yearly cost is \$ [REDACTED] (13 packs).

**Estimated PBS usage & financial implications**

- 6.35 This submission was considered by DUSC.
- 6.36 The submission estimated that if the combination of palbociclib and a NSAID is listed on the PBS, the expected uptake would be [REDACTED]% in the first year and [REDACTED]% for the four subsequent years. Increase in usage of filgrastim, a granulocyte colony stimulating factor (G-CSF), for the treatment of neutropenia associated with the usage of palbociclib was also included in the financial estimates.
- 6.37 DUSC noted that the submission attempted the triangulation of market share and epidemiological approaches in order to validate the reliability of its financial estimates. Applying the market share approach was limited by a lack of accurate cancer stage data which resulted in substantially larger estimates than the epidemiological method. DUSC agreed that the use of an epidemiological approach for the base case was appropriate.

Table 10: Estimated cost of palbociclib plus NSAID expenditure

	Year 1 2017	Year 2 2018	Year 3 2019	Year 4 2020	Year 5 2021	Source
<b>Estimated extent of use<sup>1</sup></b>						
Number treated						
Market share						
Scripts <sup>3</sup>						
<b>Utilisation of palbociclib plus NSAID<sup>2</sup></b>						
Packs of palbociclib						Table E.22 of submission
Packs of NSAID						
Packs of NSAID excluding under-copay scripts (100%-37.7%)						Medicare statistics
<b>Effective cost of palbociclib in combination with a NSAID (\$)<sup>2</sup></b>						
Palbociclib (\$ )	\$	\$	\$	\$	\$	Proposed
NSAID (\$36.15)	\$	\$	\$	\$	\$	PBS
Total palbociclib + NSAID (dispensed)	\$	\$	\$	\$	\$	-
<b>Effective cost of palbociclib in combination with a NSAID to PBS/RPBS (excluding under co-pay scripts) (\$)<sup>2</sup></b>						
Palbociclib (\$ )	\$	\$	\$	\$	\$	Proposed
NSAID (\$36.15)	\$	\$	\$	\$	\$	PBS
Total palbociclib + NSAID (dispensed)	\$	\$	\$	\$	\$	-
PBS patient co-payments (98.1% x \$5.18)	\$	\$	\$	\$	\$	Medicare statistics
RPBS patient co-payments (1.9% x \$5.07)	\$	\$	\$	\$	\$	Medicare statistics
Total patient co-payments	\$	\$	\$	\$	\$	-
<b>Net effective cost to PBS/RPBS for palbociclib + NSAID prescriptions (\$)</b>	\$	\$	\$	\$	\$	-

Source: Commentary on the main submission, Table E.2.3 page 81.

<sup>1</sup>Table E.2.5, Table E.2.6 p252 and Table E.2.10 p255 and Table E.2.11, p256 of the submission

<sup>2</sup>Submission, Table E.2.10 p. 255 and Table E.2.11, p. 256.

<sup>3</sup> Assuming 13 scripts per year as estimated by the submission.

6.38 At Year 5, the estimated number of patients was less than 10,000 per year and the net effective cost to PBS/RPBS for palbociclib + NSAID prescriptions was more than \$100 million. The total net financial cost for the PBS/RPBS for palbociclib + NSAID prescriptions was estimated to be \$50 – \$75 million in year 1, and more than \$100 million per year in the subsequent four years.

6.39 This estimate does not include the small cost of treating men with breast cancer.

6.40 The evaluation noted there is potential for the net cost/year for the PBS to be greater than the estimate in the submission given uncertainties in treatment duration due to the following factors: the median PFS as assessed by the investigators and assumed for the financial estimates was shorter than the BICR assessed PFS, the risk of treatment post-progression with palbociclib, and the potential for wastage.

6.41 DUSC noted that the assumption for the proportion of patients diagnosed with early stage disease that progress to advanced disease (23.6% over 10 years, or 3.3% annually) was based on an extrapolation of data from Kemp-Casey (2016). DUSC noted that the definition of advanced disease in this source was different to the

submission as it included progression to locally advanced disease and operable regionalised cancer. DUSC noted that basing the assumption on NSW Cancer Registry data from Lord et al. (2012), which also defined advanced cancer differently to the submission, gave an estimate of 19.9% over 10 years, or 2.0% annually. DUSC was of the view that around 21% over 10 years was a more likely estimate. This could not be readily tested as the financial estimates model only permitted set values for sensitivity analysis (19.5%, 23.6% and 24.5%).

- 6.42 DUSC considered that the assumption that 66% of total advanced breast cancer patients are HR+ / HER2-, based on Lobbezoo et al. (2013), seemed appropriate. DUSC noted that this reasonably concurred with the combined probability of 64% for HR+ (~80%) and HER2- (~80%) but considered that the estimate was more likely to be closer to 70%.
- 6.43 The requested indication of 'advanced breast cancer' may be interpreted more broadly than the intended PBS population (i.e. based on the clinical trial population including locally advanced inoperable disease that is not amenable to curative treatment with radiation, chemotherapy or surgery due to comorbidities).
- 6.44 DUSC noted that the financial estimates were highly sensitive to the assumption for time on therapy. Based on the investigator assessed median progression-free survival for the ITT population from the PALOMA-2 trial the duration of therapy was assumed to be 24.8 months (755 days). The use of a median value does not capture the survival for the whole patient cohort and DUSC considered that this gave a likely underestimate of the time on palbociclib. DUSC considered that later trial data when it is available from the sponsor on progression-free survival time and time to treatment cessation would be informative.
- 6.45 There is a high risk of treatment with palbociclib continuing post-progression or rechallenge due to the PBS restriction not specifying any conditions relating to ceasing treatment. Consequently the usage of palbociclib may be underestimated. DUSC noted the sponsor's agreement to include the following stopping rule (PSCR p1) as suggested by the PBAC Secretariat: "A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug."
- 6.46 There is the potential for use in patients who have been previously treated, or who are currently treated, with letrozole or anastrozole at the time of palbociclib's listing. This issue is likely to be most relevant for the first year of listing. There is no evidence for use in this group and it is not accounted for in the submission's estimates. The proposed treatment criteria in the restriction preclude patients who have previously received endocrine-based therapy.
- 6.47 The PSCR (p1) notes that there are patients currently accessing palbociclib who would be grandfathered to subsidised treatment. These additional patients will need to be factored into the financial estimates.
- 6.48 DUSC considered that the compliance assumptions from the PALOMA trials of ■% for palbociclib and ■% for letrozole were conservative and were likely to be overestimated.

- 6.49 Overall, DUSC considered the estimates presented in the submission to be underestimated.
- 6.50 To address the concerns of DUSC, the pre-PBAC response:
- agreed with DUSC that the PBS indication could be “locally advanced inoperable or metastatic”.
  - presented a summary of measures for treatment duration and PFS from PALOMA-1 and PALOMA-2, and stated the sponsor is willing to work with the Department of Health to develop a risk sharing arrangement based on the agreed utilisation.
  - provided sensitivity analyses to account for the prevalent population in Year 1 (i.e. the potential impact of patients on existing endocrine therapy moving to palbociclib, Scenario 1), reducing the recurrence rate to 21% (Scenario 2), and increasing ER+/HER2- to 70% (Scenario 3) in line with the DUSC advice.
  - stated approximately [REDACTED] patients would likely be eligible for grandfathering, but it is not possible to estimate the number of patients currently purchasing palbociclib from international pharmacies, via the TGA SAS process.
- 6.51 Table 11 presents patient numbers and the cost to the PBS when incorporating scenarios 1, 2 and 3 and also accounting for the potential inclusion of grandfathered patients (as estimated by the sponsor).

**Table 11: Sensitivity analyses performed by the sponsor and the DUSC Secretariat**

Step	Parameter	Year 1	Year 2	Year 3	Year 4	Year 5
0	<b>Base case</b>					
	Number of patients initiated onto palbociclib + NSAID	■	■	■	■	■
	Overall Net Cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
1	<b>Prevalent population year 1</b>					
	Number of patients initiated onto palbociclib + NSAID	■	■	■	■	■
	Overall Net Cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
2	<b>Recurrence rate reduced to 21%</b>					
	Number of patients initiated onto palbociclib + NSAID	■	■	■	■	■
	Overall Net Cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
3	<b>ER+/HER- increased to 70%</b>					
	Number of patients initiated onto palbociclib + NSAID	■	■	■	■	■
	Overall Net Cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
4	<b>Applying both 2 and 3</b>					
	Number of patients initiated onto palbociclib + NSAID	■	■	■	■	■
	Overall Net Cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
5	<b>Applying 1, 2 and 3</b>					
	Number of patients initiated onto palbociclib + NSAID	■	■	■	■	■
	Overall Net Cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
6	<b>Applying 1, 2 and 3 and including ■ grandfathered patients in Year 1</b>					
	Number of patients initiated onto palbociclib + NSAID	■	■	■	■	■
	Overall Net Cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
7	<b>Applying 2 and 3 and including ■ grandfathered patients in Year 1</b>					
	Number of patients initiated onto palbociclib + NSAID	■	■	■	■	■
	Overall Net Cost to PBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■

Source: pre-PBAC response with additional analyses by the DUSC Secretariat.

6.52 Applying the assumptions of a recurrence rate of 21% and 70% of patients being HR+/HER2- and including less than 10,000 grandfathered patients in Year 1 (approximating the patient population being treated under the proposed restriction), the net cost to PBS in year 5 was estimated to be more than \$100 million and over 5 years was estimated as more than \$100 million (Step 7, Table 11), with 10,000 – 50,000 patients initiating treatment with palbociclib + NSAID. This included the drug costs for palbociclib+letrozole and filgrastim and the costs to manage serious

adverse events based on the public cost weight AR-DRG for malignant breast disorders.

- 6.53 Including Scenario 1 (the prevalent population in Year 1, which includes patients on existing endocrine therapy moving to palbociclib, as also requested in the submission, see Section 2 Requested Listing), the net cost to PBS over 5 years was estimated as more than \$100 million (Step 6, Table 11) with approximately additional less than 10,000 patients estimated to be initiated on palbociclib in Year 1.

### **Quality Use of Medicines**

- 6.54 The submission proposed to provide education to healthcare professionals (especially oncologists and nurses) and conduct post-marketing surveillance.
- 6.55 The DUSC noted that the dosage regimen for palbociclib is 21 consecutive days followed by 7 days off treatment, comprising a complete cycle of 28 days. There is a risk of accidental continuation if it is unclear to patients that they must take a break from treatment within each cycle. However DUSC noted that the target population would be subject to intense monitoring and as such there would be other opportunities to advise patients on the use of their medicines in addition to the point of dispensing.
- 6.56 The sponsor's pre-PBAC response stated that a dosing guide and therapy management guide will be produced for healthcare professionals. A patient handbook containing a side-effect diary, complete blood count reminder card and dosing tracker will be produced.

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

- 6.57 The submission acknowledged that a volume-based risk sharing arrangement may be required, but declined an outcome-based risk share agreement based on a comparison of the projected and actual overall survival data from the PALOMA-2 trial, which will be available in 2020. No further details are provided. The pre-PBAC response stated that Sponsor is willing to work with the Department of Health to develop a risk sharing arrangement based on the agreed utilisation assumptions.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of palbociclib on the PBS as initial endocrine-based therapy for hormone receptor positive (HR+), HER2-negative (HER2-) advanced breast cancer on the basis that the PBAC did not know the circumstances in which palbociclib would be registered for use in Australia by the TGA at the time of its consideration of the submission. The PBAC noted that single agent endocrine therapy as first-line therapy is associated with significant clinical benefits in most patients and the addition of palbociclib increases the toxicity of treatment with an uncertain effect on overall survival. It was uncertain which patients would most benefit from the addition of palbociclib to a first line non-steroidal aromatase inhibitor (NSAI). Combination first line treatment which included palbociclib had a high and uncertain cost-effectiveness. Additionally, the PBAC was

of the view that the likely net cost of listing palbociclib to the PBS would be more than \$100 million over the first five years, and as such, there would be a significant opportunity cost to the Commonwealth. The PBAC noted that there are a range of effective second-line therapies (including oral agents).

- 7.2 The PBAC noted that the evaluation of palbociclib was on-going with the TGA at the time of the Committee's consideration of the submission. The TGA view immediately before the PBAC meeting was that the TGA Delegate was not in a position to recommend the approval of palbociclib in the first-line setting. The PBAC noted that it appeared that an updated Clinical Study Report for PALOMA-2 was provided to the TGA after the major submission was made to the PBAC, and it was unclear if the same data cut-offs for this trial were provided to the TGA and PBAC.
- 7.3 The PBAC noted the proposed restriction in the submission and the view of the two sub-committees and the sponsor (in their PSCR and pre-PBAC responses) on the restriction. The PBAC agreed with the ESC and DUSC that 'advanced breast cancer' may be interpreted differently between clinicians, and that a clearer definition of the population for subsidised treatment would be appropriate to avoid leakage into a broader population. The PBAC agreed with DUSC that a PBS indication of 'locally advanced inoperable and metastatic breast cancer' was consistent with the evidence provided in this submission.
- 7.4 The PBAC considered the clinical criteria of 'The treatment must be in combination with a non-steroidal aromatase inhibitor', and 'A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug' were appropriate. In addition, in line with the PALOMA-2 trial, the PBAC considered the restriction should include the criteria for use in patients with an ECOG performance status 0-2.
- 7.5 The PBAC recalled its previous recommendation to amend the PBS restrictions for five endocrine therapies for breast cancer to allow males to access subsidised treatment, when the criteria 'The patient must be postmenopausal' was replaced with 'Patient must not be pre-menopausal'. The PBAC considered similar wording would be appropriate for a listing of palbociclib.
- 7.6 The PBAC noted that the submission requested that patients who are currently well-managed with a NSAI (letrozole or anastrozole) should also be able to access the addition of palbociclib to their NSAI regimen at the time of PBS-listing. While it may be reasonable to expect that the addition of palbociclib may provide a clinical benefit to the prevalent pool of patients being treated with NSAI, the PBAC considered it was not appropriate to include this population in a listing at this time, as there is no evidence of the size of the benefit or the adverse effect profile of palbociclib in this patient population.
- 7.7 The PBAC considered that palbociclib with an NSAI would typically be used in initial endocrine treatment of patients with HR+ HER2 negative advanced breast cancer. The PBAC agreed with the ESC that NSAI alone was the appropriate comparator.
- 7.8 The PBAC noted that the submission was based on two head-to-head RCTs comparing palbociclib + letrozole to letrozole alone (PALOMA-1, n= 165 and PALOMA-2, n= 666). The submission primarily relied on PALOMA-1 because the data set was more mature. The PBAC noted the issues in the trial design and

significant risk of bias of PALOMA-1 raised by ESC. Though the predictable adverse event profile of palbociclib may also bias assessment of clinical response and patient reported outcomes in a blinded trial, the PBAC considered that data from PALOMA-2 would be more informative in evaluating the comparative efficacy and safety of palbociclib.

- 7.9 The PBAC noted that both trials showed improvement in PFS. The PBAC noted that in both trials the rate of progression was faster, and the extent of the improvement was greater, for the analyses based on the investigator assessment compared with the blinded independent central review (BICR) assessment. The PBAC noted the issues associated with the BICR outcome due to treatment decisions, including treatment cessation, being based on investigator rather than BICR assessed PFS, and increased censoring. The PBAC however stated its preference that the base case economic model be based on BICR PFS, as a less-biased estimate of incremental effectiveness.
- 7.10 The PBAC noted that the OS reported for PALOMA-1 was not significantly different, though numerically different in the favour of palbociclib. Overall survival has not yet been [REDACTED] reported for PALOMA-2, [REDACTED].
- 7.11 The submission claimed that palbociclib plus letrozole had superior comparative effectiveness to letrozole (or anastrozole) and a slightly worse but manageable safety profile. The PBAC noted the issues raised in the evaluation and by ESC. The PBAC noted the increased PFS reported in the trials, but considered the overall comparative clinical benefit of palbociclib remained unclear in the absence of evidence of a survival benefit or patient-reported improvements in their quality of life, and given the data indicating excess adverse events. The PBAC considered that use of palbociclib with letrozole had an inferior safety profile to use of letrozole alone. In addition, the PBAC noted that many women with advanced breast cancer are managed effectively on hormone therapy only and the next line chemotherapies include well-tolerated oral therapies, and therefore the benefit of palbociclib in delaying time to chemotherapy is uncertain, particularly given that palbociclib itself is associated with significant toxicities.
- 7.12 The PBAC noted that in both PALOMA-1 and PALOMA-2, substantially more patients treated with palbociclib + letrozole reported AEs compared with those treated with letrozole alone. Of note, more patients treated with palbociclib + letrozole had grade  $\geq 3$  AEs, temporarily discontinued treatment due to AEs, discontinued treatment altogether or had a dose reduction. The PBAC noted that across the two trials, approximately 74% patients would experience neutropenia, and a higher number of patients would experience troublesome symptoms such as fatigue. There was an increased risk of febrile neutropenia in PALOMA-2, The PBAC considered that the submission's comparative safety claim of 'a slightly worse but manageable safety profile' understated the toxicity of palbociclib, and that this was particularly important for a chronic oral therapy.
- 7.13 The PBAC raised a number of concerns regarding the structure of the economic model and its inputs, and considered that the sponsor's revised ICER of \$45,000/QALY – \$75,000/QALY was substantially underestimated. The concerns

included:

- It was inappropriate to base the economic model on investigator assessed PFS from PALOMA-1, which is potentially subject to bias compared to BICR, and OS from PALOMA-1, which was immature and not statistically significant different between the treatment arms. The PBAC rejected the justification from the sponsor that using the PFS from PALOMA-1 increases internal validity as the OS data were also from PALOMA-1, and required less extrapolation as the duration of follow-up was longer in PALOMA-1 than PALOMA-2. The PBAC considered that the BICR assessed PFS of PALOMA-2 was more appropriate data to inform the base case model.
- The PBAC agreed with the ESC that the submission underestimated the cost of providing palbociclib. The PBAC considered the palbociclib cost should be based on the mean treatment duration, and the calculations in the model were incorrect due to not including, costs beyond 22 cycles.
- It was appropriate to include the cost of letrozole in both arms of the model, rather than assume the cost is the same in both arms.
- The time horizon of 10 years applied in the economic model was too long given the available clinical evidence. The PBAC noted that the pre-PBAC response reiterated the survival rate of approximately 10% at 10-years in HR+/HER2- advanced breast cancer, but the PBAC considered a shorter time horizon was appropriate given the immaturity of the existing OS data and that any increase in OS was uncertain at the moment. The PBAC recalled that in previous submissions for advanced breast cancer, although for later line treatment, the time horizon was 3 years (everolimus, 2013 and paclitaxel, 2008).
- The PBAC considered that it would be more robust for the extrapolation to occur from an earlier point of the Kaplan-Meier curves at a time point where the observed data are not unreliable. The PBAC considered in this case extrapolating from the point of median follow-up would be appropriate. The PBAC also noted that it may be more appropriate to extrapolate the OS data in the submission using a Weibull function rather than log-logistic function based on the goodness of fit. In addition, the extrapolation approach assumed that the treatment effect persists for the model duration, which the PBAC considered was an inappropriate assumption.
- The PBAC noted the error with the estimated post-progression costs that was identified during the evaluation, and the re-specification of post-progression costs in the PSCR. The PBAC agreed with ESC that it was not clear which source of cost was reasonable to apply to the economic model at this time. Not accepting the argument in the pre-PBAC response about the post-progression cost from Verry et al (2012), the PBAC considered that post-progression costs need to be fully accounted for and up-to-date.
- Given the safety profile of palbociclib, costs and quality of life impacts for adverse events should be more systematically applied in the economic model. The PBAC considered it was appropriate to at least include all serious adverse events in the model rather than only treatment-related events. The PBAC noted that the increased risk of febrile neutropenia in PALOMA-2 and while the risk is small, the PBAC considered it was important and should be included in economic model.

Overall, these issues left the PBAC with considerable uncertainty as to the estimation of the cost-effectiveness of palbociclib + NSAI.

- 7.14 The PBAC noted that, after addressing most concerns of DUSC in regards to the size of the patient population and including the sponsor's estimate of [REDACTED] patients who would likely be eligible for grandfathering, the net cost to PBS over 5 years was more

than \$100 million over 5 years. The PBAC considered that usage and financial impact remained likely to be underestimated, due to:

- The likelihood that average treatment duration with palbociclib will be longer than the estimate from PALOMA-2 (median PFS of 24.8 months).
- The risk of treatment with palbociclib continuing post-progression even with a restriction specifying conditions relating to ceasing treatment.
- The potential for use in patients being treated with letrozole or anastrozole at the time of palbociclib's listing (i.e. the prevalent pool of patients). Sensitivity analysis suggested an additional cost of approximately \$30 – \$60 million across Year 1 and Year 2 of the estimates.
- Due to the different avenues through which patients may currently access palbociclib, the size of patient population who would likely be eligible for grandfathering may be greater than approximately less than 10,000, as stated in the pre-PBAC response.

Some of these uncertainties could be managed in a risk-share agreement between the Commonwealth and the sponsor.

- 7.15 The PBAC noted that breast cancer is the most common cancer in females and that the majority of patients with advanced breast cancer patients have the HR+ / HER2-type (approximately 70% based on DUSC advice). The PBAC welcomed the comments received via the Consumer Comments facility on the PBS website. The PBAC noted an editorial by AC Wolff in the New England Journal of Medicine (2016; 375:1993)

The PBAC was concerned, notwithstanding the on-going TGA evaluation, that the submission's currently reported efficacy (though no demonstrated overall survival) and harms had not yet identified the patient population who would gain most benefit nor justified the approach to estimating the cost-effectiveness of this treatment on the PBS, at the price proposed by the sponsor.

- 7.16

The PBAC considered that this crude comparison between treatments was not informative, as it only focuses on only one of the clinical aspects of submissions assessed by the PBAC and it was not based on the actual cost to Government for the PBS-listed treatments.

- 7.17 The PBAC would welcome a major resubmission for palbociclib, addressing the concerns of the PBAC, ESC and DUSC; and when more information is known on the conditions of registration of palbociclib in Australia, and further outcome data is available from PALOMA-2, particularly relating to overall survival. The PBAC considered that, given the complexities of this submission, exploring uncertain assumptions in sensitivity analysis of the economic model would be informative for decision making.

- 7.18 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**

Worldwide, over 50,000 patients have been treated with palbociclib following its first regulatory approval on 3 February 2015 in the United States. In Australia, palbociclib received regulatory approval on 3 May 2017. It has been 18 years since the most recent initial endocrine treatment for locally advanced or metastatic HR-positive, HER2-negative breast cancer was listed on the PBS and consequently there has been little advancement in the standard of care of these patients in recent times.

Palbociclib, in combination with a non-steroidal aromatase inhibitor (letrozole or anastrozole), has demonstrated clinically important progression-free survival benefits and a manageable toxicity profile. Palbociclib delays progression and therefore delays treatment with chemotherapy and improves related survival outcomes without compromising quality of life.

Pfizer is committed to working with the PBAC and the Department of Health to make palbociclib available for these patients, without delay.