

7.06 PALBOCICLIB, Capsule 75 mg, 100 mg and 125 mg Ibrance[®], Pfizer Australia Pty Ltd

1 Purpose of application

- 1.1 Authority Required listing for palbociclib for treatment of non pre-menopausal patients with HR+/HER2- locally advanced inoperable breast cancer and metastatic breast cancer. The PBAC previously considered an application for palbociclib for this indication at the March 2017 meeting.
- 1.2 The requested basis for listing was a cost-utility analysis for palbociclib plus a non-steroidal aromatase inhibitor (NSAI) compared with a NSAI alone. This is unchanged from the previous submission.

Table 1: Key components of the clinical issue addressed by the re-submission

Component	Description
Population	Non pre-menopausal patients with hormone receptor positive (HR+)/ human epidermal growth factor receptor 2 negative (HER2-) locally advanced inoperable breast cancer and metastatic breast cancer
Intervention	Palbociclib (125 mg on days 1-21 of a 28-day cycle) + NSAI
Comparator	Non-steroidal aromatase inhibitor
Outcomes	Progression-free survival Overall survival Overall response rate Health related quality of life Serious adverse events
Clinical claim	Superior comparative effectiveness to letrozole (or anastrozole) as the main comparator and a worse but manageable safety profile

Source: Compiled during evaluation

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.

Public Summary Document – November 2017 PBAC Meeting

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	\$ [REDACTED] (effective) \$ [REDACTED] (published)	Ibrance® Pfizer Australia

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	
Severity:	Advanced Locally advanced or metastatic
Condition:	Breast cancer
PBS Indication:	Locally advanced inoperable breast cancer and or metastatic breast cancer
Restriction Level / Method:	<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
Treatment criteria:	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.
Clinical criteria:	The condition must be hormone receptor positive, AND The condition must be human epidermal growth factor receptor 2 (HER2) negative, AND <i>The condition must be inoperable</i> AND Patient must have a ECOG WHO performance status of 0 to 2 AND <i>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)</i>
Population criteria:	Patient must not be pre-menopausal
Prescriber Instructions	<i>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug</i> 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>Administrative Advice</p>	<p><i>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:</i> <i>Complete response (CR) is disappearance of all target lesions.</i> <i>Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.</i> <i>Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.</i> <i>Stable disease (SD) is small changes that do not meet above criteria.</i></p> <p>No applications for increased maximum quantities will be authorised.</p> <p>No applications for increased repeats will be authorised.</p> <p>Special Pricing Arrangements apply.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Note</p>	<p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS subsidised treatment with this drug</p>

- 2.2 The recommended dose regimen for palbociclib is a 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.
- 2.3 The re-submission included a note within the PBS restriction that patients whose disease progressed on palbociclib would no longer be eligible for PBS-subsidised palbociclib. This is changed from the previous submission, in line with the PBAC's previous consideration. However, there is a risk of treatment with palbociclib continuing post-progression even with a restriction specifying conditions relating to ceasing treatment (Public Summary Document (PSD), March 2017, item 7.4 and 7.14).
- 2.4 The re-submission included a restriction relating to World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) status. This is changed from the previous submission, in line with the PBAC's previous consideration (PSD, March 2017, item 7.4).
- 2.5 The re-submission again requested that the PBAC consider whether patients who are currently well managed with a NSAID (letrozole or anastrozole) should also be able to access the addition of palbociclib to their NSAID regimen at the time of PBS-listing (a prevalent pool of patients).
- 2.6 The re-submission (and reiterated in the Pre-Sub-Committee-Response (PSCR), p3) requested that patients who are being treated with palbociclib prior to PBS-listing be

grandfathered to receive PBS-subsidised treatment with this drug. The re-submission stated that 500 patients would likely be eligible for grandfathering in Year 1. The re-submission did not propose the text for a Grandfather restriction, nor discuss why these patients would be unable to access treatment with the proposed restrictions. The pre-PBAC response stated that in Australia, the sponsor has included more than 250 advanced breast cancer patients in clinical trials of palbociclib and is currently recruiting up to 300 patients in clinical trials of palbociclib for other forms of breast cancer.

- 2.7 The re-submission proposed an effective price for palbociclib that is ■■■% lower than the previous submission.
- 2.8 The economic model and financial forecasts in the re-submission included the assumption that up to 10% of patients would be treated with of filgrastim, a granulocyte colony stimulating factor (G-CSF), for the treatment of neutropenia associated with the usage of palbociclib. While this assumption is discussed below, the PSCR (p 3) requested that the PBAC may wish to consider whether the current PBS streamlined authority restrictions for filgrastim should be expanded to capture rare, unresolved occurrences of CDK4/6 inhibitor-induced high grade neutropenia.

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

3 Background

Registration status

- 3.1 Palbociclib was TGA registered on 3 May 2017 for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:
 - an aromatase inhibitor as initial endocrine-based therapy;
 - fulvestrant in patients who have received prior therapy.

Previous PBAC consideration

- 3.2 In March 2016 the PBAC did not recommend the listing of palbociclib on the PBS as initial endocrine-based therapy for HR+/HER2- advanced breast cancer on the basis that at the time of its consideration the PBAC did not know the circumstances in which palbociclib would be registered for use in Australia by the TGA. 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 NSAI. Combination first line treatment that 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) (PSD, March 2017, item 7.1).

3.3 A summary of the outstanding matters of concern to the PBAC are provided in the table below.

Table 2: Summary of outstanding matters of concern

Matters of concern	How the resubmission addresses it
<p>Regulatory status 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’s 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. (PSD, March 2017, item 7.2)</p>	<p>Palbociclib was registered on the Australian Register of Therapeutic Goods (ARTG) on 3rd May 2017</p>
<p>PALOMA-1 open-label design 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. (PSD, March 2017, item 7.8). 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: <ul style="list-style-type: none"> • 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. (PSD, March 2017, item 6.7).</p>	<p>Fitted log-logistic functions to investigator-assessed PFS in PALOMA-2 to inform transition probabilities associated with progression. Also fitted log-logistic functions to updated OS from PALOMA-1 to inform transition probabilities associated with death</p>
<p>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. (PSD, March 2017, item 7.9).</p>	<p>The re-submission argued that investigator-assessed PFS is appropriate to apply in the economic model</p>
<p>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 formally reported for PALOMA-2 (PSD, March 2017, item 7.10).</p>	<p>Provided updated OS (as of 30 December 2016) results for PALOMA-1. Did not provide updated OS results for PALOMA-2. [REDACTED]</p>
<p>Clinical claim –efficacy The submission claimed that palbociclib plus letrozole had superior comparative</p>	<p>Clinical claim unchanged</p>

Matters of concern	How the resubmission addresses it
<p>effectiveness to letrozole (or anastrozole).</p> <p>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. (PSD, March 2017, item 7.11-12).</p>	
<p>Clinical claim – safety</p> <p>The submission claimed that palbociclib plus letrozole had a slightly worse but manageable safety profile to letrozole (or anastrozole).</p> <p>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 ≥ 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. (PSD, March 2017, item 7.11-12).</p>	<p>Clinical claim changed to a worse but manageable safety profile.</p>
<p>Economic evidence –efficacy data</p> <p>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. (PSD, March 2017, item 7.13)</p>	<p>Fitted log-logistic functions to investigator-assessed PFS in PALOMA-2 to inform transition probabilities associated with progression. Also fitted log-logistic functions to updated OS from PALOMA-1 to inform transition probabilities associated with death.</p>
<p>Economic evidence – duration of treatment with palbociclib</p> <p>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. (PSD, March 2017, item 7.13)</p>	<p>Duration of treatment with palbociclib changed to 27 cycles (median PFS from PALOMA-2). Usage beyond 27 cycles remains inappropriately truncated.</p>
<p>Economic evidence – cost of letrozole</p> <p>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. (PSD, March 2017, item 7.13)</p>	<p>The re-submission included the costs for letrozole and anastrozole to both the comparator and the palbociclib arms. Previously these costs were excluded.</p>
<p>Economic evidence – time horizon</p> <p>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,</p>	<p>Time horizon (10 years) unchanged.</p>

Matters of concern	How the resubmission addresses it
<p>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). (PSD, March 2017, item 7.13).</p>	
<p>Economic evidence – extrapolation 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. (PSD, March 2017, item 7.13).</p>	<p>The PFS and OS Kaplan-Meier trial data from PALOMA-1 and PALOMA-2 were not directly applied in the economic model. Instead the re-submission estimated PFS and OS using only fitted parametric (log-logistic) functions for the entire time horizon. The assumption regarding treatment effect was unchanged.</p>
<p>Economic evidence – Post-progression treatment costs 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. (PSD, March 2017, item 7.13).</p>	<p>Updated pre-progression and post-progression costs.</p>
<p>Economic evidence – adverse events 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. (PSD, March 2017, item 7.13).</p>	<p>Included hospitalisation costs for treatment related SAEs.</p>
<p>Financial estimates The PBAC considered that usage and financial impact remained likely to be underestimated, due to:</p> <ul style="list-style-type: none"> • 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). • Due to the different avenues through which patient's may currently access palbociclib, the size of patient population who would likely be eligible for grandfathering may be greater than approximately 500, as stated in the pre-PBAC response. <p>(PSD, March 2017, item 7.14).</p>	<p>The re-submission included a note within the PBS restriction that patients whose disease progressed on palbociclib would no longer be eligible for PBS-subsidised palbociclib. The re-submission (and reiterated in the PSCR) added grandfathered patients in the financial estimates and requested a Grandfather restriction.</p>

AE: Adverse event. PFS: Progression-free survival. SAE: Serious adverse event.

3.4 Ribociclib, a near market comparator, was also considered by the PBAC in July 2017 for the first-line endocrine treatment of hormone receptor HR+, HER2- advanced

breast cancer (ABC) in combination with letrozole. At the meeting, the PBAC did not recommend the listing of ribociclib on the PBS as initial endocrine-based therapy for patients with non pre-menopausal, hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer on the basis of unfavourable and uncertain cost-effectiveness, and uncertainties regarding the effect of ribociclib on overall survival based on the data presented in the submission. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was unacceptably high, noting that this was largely driven by the high cost of ribociclib. A major re-submission was considered by the PBAC for a similar indication at the November 2017 meeting.

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

4 Population and disease

- 4.1 Breast cancer is among the most commonly diagnosed cancers in Australia. The most common form of breast cancer is the HR+/HER- molecular subtype, which is associated with favourable prognosis due to its responsiveness to hormonal/endocrine therapy. However, development of endocrine resistance may limit the efficacy of current therapies, which eventually leads to disease progression.
- 4.2 The re-submission proposed the addition of palbociclib, in combination with a NSAI, for the treatment of non pre-menopausal patients with HR+/HER2- locally advanced inoperable breast cancer and metastatic breast cancer. While palbociclib was proposed for listing and registered in combination with any NSAI, the clinical evidence presented in the re-submission was specific to a particular NSAI (letrozole).

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

5 Comparator

- 5.1 The comparator provided in the resubmission was NSAI (letrozole or anastrozole) alone. This is unchanged from the previous submission. The PBAC previously considered that this is the appropriate comparator.
- 5.2 The ESC considered that it would be appropriate to consider ribociclib as a near market comparator, which was on the agenda for a similar indication at the November 2017 meeting.

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 individuals (115), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments were similar to those received when the original palbociclib submission was considered, and described a range of benefits of treatment with palbociclib including the ability to return to work and live active lives, improved quality of life, manageable side effects, slowed disease progression and delayed time to chemotherapy, but its very high financial cost was also noted. Many comments stated that there was a need for affordable and fair access to new and innovative cancer treatments. The PBAC noted the significant increase in consumer responses compared to when palbociclib was last considered.
- 6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) supporting the listing of palbociclib. The PBAC specifically noted the claim that the use of palbociclib may improve quality of life and result in time and financial savings to both the health system and patients. The BCNA also noted evidence presented at the recent American Society of Clinical Oncology (ASCO) Annual Scientific Meeting that showed all women treated with palbociclib in the PALOMA-2 clinical trial benefited from the treatment, including those with visceral disease.
- 6.4 The Medical Oncology Group of Australia (MOGA) expressed its support for the palbociclib submission, based on improved progression free survival (PFS). The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for palbociclib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)^[1], based on a comparison with NSAI alone. The MOGA noted that if future analysis demonstrates a survival benefit for palbociclib in combination with letrozole, the ESMO-MCBS score may increase to 4.

Clinical trials

- 6.5 The re-submission was based on two head-to-head trials comparing palbociclib + letrozole to letrozole alone:
- PALOMA-1: an open-label, multicentre, phase II RCT for first line treatment of ER+, HER2- advanced breast cancer (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.
- 6.6 Details of the trials presented in the re-submission are provided in the table below. An independent search located no other relevant trials, but did identify several additional citations of the trials presented in the previous submission.

^[1] [1] 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 3: Trials and associated reports presented in the re-submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
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.	30 July 2015.
	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.	The Lancet 2015; 16:25-35.
	Finn, RS Crown, JP Lang, I et al. Overall survival results from the randomized phase II study of palbociclib (P) in combination with letrozole (L) vs letrozole alone for frontline treatment of ER+/HER2-advanced breast cancer (PALOMA-1; TRIO-18).	2017 ASCO Meeting, J Clin Oncol 35, 2017 (suppl; abstr 1001)
	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.	Breast Cancer Research (2016) 18:67.
	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.	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.	11 August 2016
	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).	J Clin Oncol 34, 2016 (suppl; abstract 507).
	Finn R., Jiang Y, Rugo H et al. Biomarker analyses from the phase 3 PALOMA-2 trial of palbociclib (P) with letrozole (L) compared with placebo (PLB) plus L in postmenopausal women with ER + /HER2-advanced breast cancer (ABC).	Annals of Oncology. Conference: 41 st European Society for Medical Oncology Congress, ESMO 2016. Denmark. 27 (no pagination), 2016. Date of Publication: 2016.
	Rugo H, Dieras V, Gelmon K.A et al. Impact of palbociclib plus letrozole on health related quality of life (HRQOL) compared with letrozole alone in treatment naive postmenopausal patients with ER+ HER2-metastatic breast cancer (MBC): Results from PALOMA-2.	Annals of Oncology. Conference: 41 st European Society for Medical Oncology Congress, ESMO 2016. Denmark. 27 (no pagination), 2016. Date of Publication: 2016.
	Ruiz A., Gauthier E., Durairaj C et al. Evaluation of the effects of palbociclib (PAL) letrozole (LET) on Tc.	Cancer Research. Conference: 39 th Annual CTRC-AACR San Antonio Breast Cancer Symposium. United States. 77 (4 Supplement 1) (no pagination), 2017. Date of

Trial ID/First Author	Protocol title/ Publication title	Publication citation
		Publication: February 2017.
	Finn, RS Dieras, V Rugo HS et al. Palbociclib (PAL) + letrozole (L) as first-line (1L) therapy (tx) in estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): Efficacy and safety across patient (pt) subgroups.	2017 ASCO Meeting, J Clin Oncol 35, 2017 (suppl; abstr 1039)

Source: Table B.2.2 p31 of the re-submission.

6.7 The key features of the direct randomised trials are summarised in the table below. The median duration of follow-up in PALOMA-1 increased from the previous submission (from 29.6 months for palbociclib + letrozole, and 27.9 months for letrozole alone).

Table 4: Key features of the included evidence, palbociclib plus letrozole vs. letrozole alone

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
PALOMA-1	165	R, OL 64.7 months	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: 23.0 mths L: 22.3 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 based on p41-48 and p52-53 of the re-submission.

6.8 The PBAC previously noted the issues in the trial design and significant risk of bias of PALOMA-1 arising from the open-label design. 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 (PSD, March 2017, item 7.8).

Comparative effectiveness

6.9 Figures 1 to 4 demonstrate the difference between the investigator-assessed and the Blinded Independent Central Review (BICR) assessed PFS. These figures are unchanged from the previous submission.

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

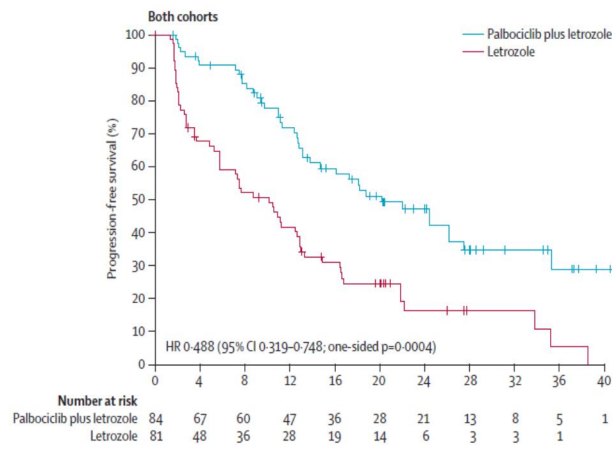
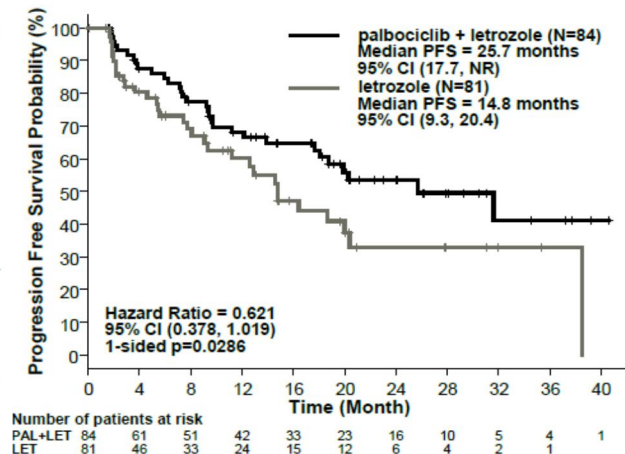


Figure 2: PALOMA-1 Kaplan-Meier Plot of PFS – BICR (ITT Population)



BICR: Blinded Independent Central Review. ITT: Intent-to-treat. PFS: Progression-free survival. Source: Figure B.6.1 p71 and Figure B.6.2 p73 of the re-submission

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

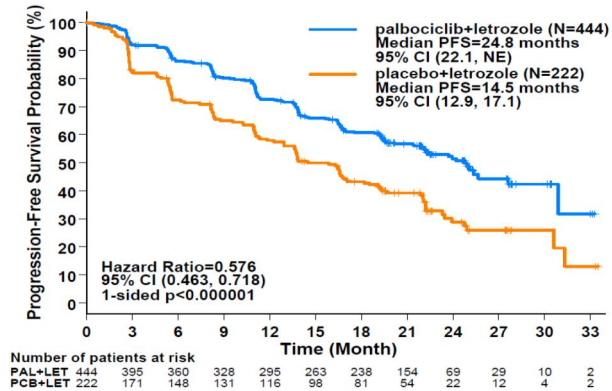
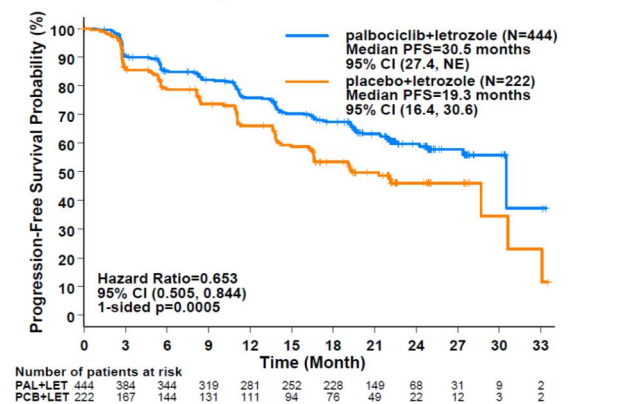


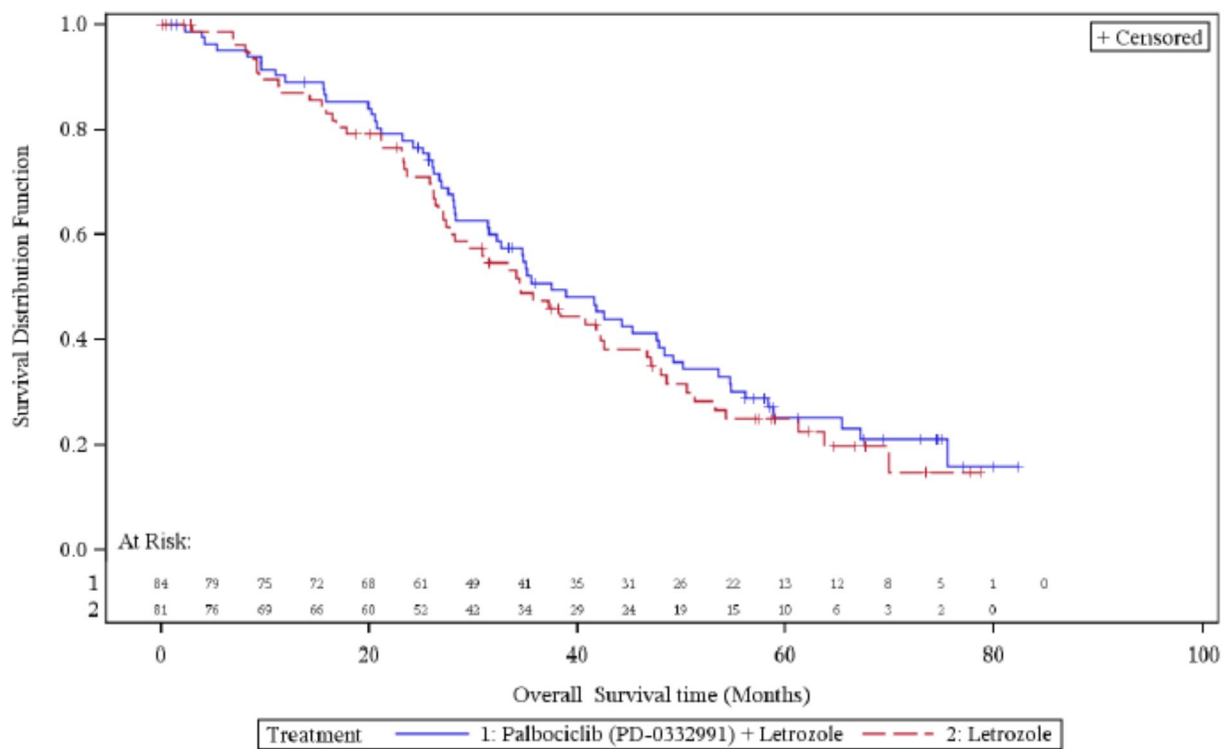
Figure 4: PALOMA-2 Kaplan-Meier Plot of PFS – BICR (ITT Population)



BICR: Blinded Independent Central Review. ITT: Intent-to-treat. PFS: Progression-free survival. Source: Figure B.6.10 p91 and Figure B.6.13 p98 of the re-submission

6.10 Figure 5 demonstrates the OS difference between palbociclib + letrozole and letrozole alone in PALOMA-1 based on updated data. This is changed from the previous submission. The ESC considered that these data suggest that palbociclib + letrozole is not associated with an increase in OS compared with letrozole alone.

Figure 5: Updated PALOMA-1 Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) (30 December 2016)



Source: Figure B.6.5 p80 of the re-submission

6.11 The key results from the direct randomised trials are presented in the table below.

Table 5: Results of PFS and OS 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)
PFS						
PALOMA-1 (29 November 2013) ^a						
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 ^d (0.319, 0.748) 1-sided p-value 0.0004 ^e
BICR	31/84 (36.9)	33/81 (40.7)	25.7 (17.7, NR)	14.8 (9.3, 20.4)	10.9	HR 0.621 ^d (0.378, 1.019) 1-sided p-value ^e 0.0286
PALOMA-2 (26 February 2016) ^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 ^d (0.463, 0.718) 1-sided p-value <0.000001 ^e
BICR	152/444 (34.2)	96/222 (42.3)	30.5 (27.4, NR)	19.3 (16.4, 30.6)	11.2	HR 0.653 ^d (0.505, 0.844) 1-sided p-value 0.000532 ^e
Overall survival						
PALOMA-1						
29 November 2013 ^a	30/84 (35.7)	31/81 (38.3)	37.5 (28.4, NR)	33.3 (26.4, NR)	4.2	HR 0.813 ^d (0.492, 1.345) 1-sided p-value 0.2105 ^e
30 December 2016 ^c	60/84 (71.4)	56/81 (69.1)	37.5 (31.4, 47.8)	34.5 (27.4, 42.6)	3.0	HR 0.897 ^d (0.623, 1.294) 1-sided p-value 0.281237 ^e
PALOMA-2						
26 February 2016 ^b	██████████	██████████	NR	NR	NR	NR
24 November 2016 ^f	NR (27.0%)	NR (28.8%)	NR	NR	NR	NR

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

a. Median duration of follow-up = 29.6 months in the palbociclib plus letrozole arm and 27.9 months in the letrozole arm.

b. Median duration of follow-up = 23.0 months in the palbociclib plus letrozole arm and 22.3 months in the letrozole arm.

c. Median duration of follow-up = 64.7 months

d. Assuming proportional hazards

e. 1-sided p-value from the log-rank test stratified by Part.

f. Median duration of follow-up unknown.

Source: Table B.6.1 p72, B.6.2 p74, B.6.12 p92, B.6.14 p97, Table B.6.4 p77 and Table B.6.5 p79 of the re-submission and Table 49 of PALOMA-2 (A5481008) CSR Report Body.pdf and p28 of the TGA delegates overview and calculated during the evaluation.

6.12 Palbociclib resulted in a statistically significant improvement in PFS in both trials. The median difference in PFS in PALOMA-1 was 10.9 months by BICR compared to 10.0 months when investigator assessed. The median difference in PFS in PALOMA-2 was 11.2 months by BICR compared to 10.3 months when investigator assessed. The investigator assessed results appear over-estimated when compared to the BICR results. These results are unchanged from the previous submission.

6.13 The re-submission presented updated OS results for PALOMA-1. At the 30 December 2016 cut off, 71.4% of patients in the palbociclib + letrozole arm and 69.1% of patients in the letrozole alone arm had died. The difference in OS, although in favour of palbociclib (median increase of 3.0 months), was not statistically significant

(p=0.28).

- 6.14 The re-submission did not provide updated OS results from PALOMA-2. The latest data available in the PALOMA-2 clinical study report was from a February 2016 interim analysis. Final OS results from PALOMA-2 are expected in 2020. The PBAC previously expressed a preference that further outcome data from PALOMA-2, particularly relating to OS, would be valuable (PSD, March 2017, item 7.17).

Comparative harms

- 6.15 In PALOMA-1 and PALOMA-2, 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 ≥ 3 AEs (PALOMA-1: 78.3% vs. 20.8%, PALOMA-2: 79.8% vs. 27.0%). In PALOMA-1, 3.6% of patients experienced pulmonary embolism (PE) in the palbociclib + letrozole arm, compared to no cases in the letrozole arm. In PALOMA-2, 1.6% (0.2% considered treatment related) of patients experienced PE and 0.9% (0.7% considered treated related) experienced deep vein thrombosis (DVT) in the palbociclib + letrozole arm. These results are unchanged from the previous submission.
- More patients treated with palbociclib + letrozole had serious AEs (PALOMA-1: 21.7% vs. 6.5%, PALOMA-2: 19.6% vs. 12.6%). These results are unchanged from the previous submission.
- More patients treated with palbociclib + letrozole temporarily discontinued treatment due to AEs (PALOMA-1: **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). These results are unchanged from the previous submission.
- 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%). These results are unchanged from the previous submission.
- In patients treated with palbociclib + letrozole the most common AEs included neutropenia (PALOMA-1: 75% as of December 2016, PALOMA-2: 79.5%), leukopenia (PALOMA-1: 43% as of December 2016, PALOMA-2: 39.0%), fatigue (PALOMA-1: 41% as of December 2016, PALOMA-2: 37.4%) and infections (PALOMA-1: NR, PALOMA-2: 59.7%). The estimates from PALOMA-1 have been updated compared to the previous submission.
- In patients treated with palbociclib + letrozole the most common grade 3 or 4 AEs included neutropenia (grade 4) (PALOMA-1: 6% as of December 2016, PALOMA-2: 10.4%), neutropenia (grade 3) (PALOMA-1: 53% as of December 2016, PALOMA-2: 56.1%) and leukopenia (grade 3) (PALOMA-1: 18% as of December 2016, PALOMA-2: 24.1%). The estimates from PALOMA-1 have been updated compared to the previous submission.

- 6.16 The PSCR (p1) reviewed the clinical study reports (CSR) for PALOMA-1 and PALOMA-2 for reference to PE and DVT (Table 6), and also noted that these AEs are not

mentioned in the Australian product information. The sponsor stated the data from PALOMA-1 and PALOMA-2 are inconclusive in terms of risk of these AEs and the incidence of these AEs is low. The ESC noted that the incidence of these AEs were different between the two trials, but considered that there remained a risk of these AEs if this medicine is available in the broader PBS population compared to the controlled trial environment. As at its February 2017 meeting, the ESC noted patients with pulmonary embolism would require lifetime treatment with anti-coagulants. The pre-PBAC response presented the lifetime treatment costs for the oral anti-coagulant apixaban based on a median OS of 37.5 months, the incidence of PE and DVT as presented in Table 6 and the estimated number of patients treated with palbociclib in Year 5 (Table 13). For PALOMA-1, the total incremental cost of lifelong anticoagulant treatment was claimed to be \$ [REDACTED]. For PALOMA-2 a saving of \$ [REDACTED] was claimed due to the greater incidence of events observed in the letrozole arm.

Table 6: Reports of deep vein thrombosis and pulmonary embolism in PALOMA-1 and PALOMA-2

	Palbociclib + letrozole	Placebo + letrozole
PALOMA-1 (N = 165)		
Pulmonary embolism (Serious AE)	3.6%	0%
PALOMA-2 (N = 666)		
Deep Vein Thrombosis (Treatment-related AE)	0.5%	0%
Deep Vein Thrombosis (Serious AE)	0.5%	0.5%
Pulmonary embolism (Treatment-related AE)	0.2%	0.7%
Pulmonary embolism (Serious AE)	0.9%	1.4%

Reference: PSCR (p1): PALOMA-1 CSR Table 72, PALOMA-2 CSR Section 12.2.4.4.5. Venous thromboembolic disorders

6.17 The re-submission claimed that the addition of palbociclib to letrozole maintained health-related quality of life. The re-submission argued that there were no statistically significant differences between the treatment arms in PALOMA-2 measured using Functional Assessment of Cancer Therapy-Breast (FACT-B), Functional Assessment of Cancer Therapy-General (FACT-G), and the EQ-5D visual analogue scale. This is unchanged from the previous submission. The trial was not powered to detect changes in patient reported outcomes.

Benefits and harms

6.18 A summary of the comparative benefits and harms for palbociclib plus letrozole versus letrozole alone is presented in the table below.

Table 7: Summary of comparative benefits and harms for palbociclib + letrozole and letrozole alone

Benefits						
Event	Palbociclib + letrozole		Letrozole alone	RD (%)	HR (95% CI)	
PFS (investigator assessed): PALOMA-1 (29 November 2013)^a						
Event free at 12 months, % (95% CI)	71.8 (59.7, 80.9)		41.7 (30.2, 52.9)	30.1	0.488 (0.319, 0.748)	
PFS (BICR): PALOMA-1 (29 November 2013)^a						
Event free at 12 months, % (95% CI)	68.1 (55.6, 77.7)		60.1 (45.7, 71.8)	8.0	0.621 ^d (0.378, 1.019)	
PFS (investigator assessed): PALOMA-2 (26 February 2016)^b						
Event free at 12 months, % (95% CI)	72.6 (68.0, 76.6)		57.9 (50.9, 64.4)	14.7	0.576 (0.463, 0.718)	
Event free at 24 months, % (95% CI)	51.4 (45.8, 56.8)		28.8 (21.5, 36.6)	22.6		
PFS (BICR): PALOMA-2 (26 February 2016)^b						
Event free at 12 months, % (95% CI)	75.8 (71.3, 79.7)		66.1 (58.8, 72.4)	9.7	0.653 (0.505, 0.844)	
Event free at 24 months, % (95% CI)	59.7 (54.2, 64.9)		46.1(37.8, 53.9)	13.6		
OS: PALOMA-1 (30 December 2016)^c						
Survival at 12 months, % (95% CI)	89.0 (80.0, 94.1)		87.0 (77.2, 92.8)	2.0	0.897 (0.623, 1.294)	
Survival at 24 months, % (95% CI)	77.9 (67.2, 85.5)		71.1 (59.4, 79.9)	6.8		
Survival at 36 months, % (95% CI)	50.8 (39.3, 61.2)		47.4 (35.6, 58.3)	3.4		
Harms						
	Palbociclib + letrozole	Letrozole alone	RR (95% CI)	Events/100 patients		RD (95% CI)
				Palbociclib + letrozole	Letrozole alone	
Grade>3 adverse events						
PALOMA-1 ^c	65/83	16/77	3.8 (2.4, 5.9)	78.3	20.8	57.5% (44.9%, 70.2%)
PALOMA-2 ^b	354/444	60/222	3.0 (2.4, 3.7)	79.8	27.0	52.7% (45.8%, 59.6%)
Neutropenia						
PALOMA-1 (grade 3) ^c	NR	NR	53.0 (5.7, 493.7)	53	1	52.0% (41.0%, 63.0%)
PALOMA-1 (grade 4) ^c	NR	NR	-	6	0	6% (-, -)
PALOMA-2 (grade 3) ^b	249/444	2/222	62.3 (15.6, 248.0)	56.1	0.9	55.2% (50.4%, 60.0%)
PALOMA-2 (grade 4) ^b	46/444	1/222	23.0 (3.2, 165.7)	10.4	0.5	9.9% (6.9%, 12.9%)
Febrile neutropenia						
PALOMA-1 ^c	NR	NR	NR	NR	NR	NR
PALOMA-2 ^b	11/444	0/222	11.5 (0.7, 194.7) ^d	2.5	0	2.5% (1.0%, 3.9%)
Leukopenia						
PALOMA-1 ^c	43/83	4/77	10.0 (3.8, 26.5)	51.8	5.2	46.6% (34.8%, 58.5%)
PALOMA-2 ^b	173/444	5/222	17.3 (7.2, 41.5)	39.0	2.3	36.7% (31.8%, 41.6%)
Fatigue						
PALOMA-1 ^c	41/83	23/77	1.7 (1.1, 2.5)	49.4	29.9	19.5% (4.7%, 34.4%)
PALOMA-2 ^b	166/444	61/222	1.4 (1.1, 1.7)	37.4	27.5	9.9% (2.5%, 17.3%)

a. Median duration of follow-up = 29.6 months in the palbociclib plus letrozole arm and 27.9 months in the letrozole arm.

b. Median duration of follow-up = 23.0 months in the palbociclib plus letrozole arm and 22.3 months in the letrozole arm.

c. Median duration of follow-up = 64.7 months

d. adding 0.5 cases to each treatment arm.

Abbreviations: BICR= Blinded Independent Central Review; HR = hazard ratio; NR: not reported; PFS: Progression-free survival; OS: Overall survival; RR = risk ratio.

Source: Table B.6.1 p72, B.6.2 p74, Table B.6.4 p77, Table B.6.5 p79, B.6.12 p92, B.6.14 p97, Table B.6.29 p120, Table B.6.31 p123, Table B.6.36 p131, Table B.6.37 p133, and Figure B.6.31 p123 of the re-submission and Table 27, 28 of PALOMA-1 (A5481003) CSR Report Body.pdf, p1 of A5481003 Updated OS Analysis.pdf, Table 20, Table 23, Table 49 of PALOMA-2 (A5481008) CSR Report Body.pdf and calculated during the evaluation.

6.19 On the basis of direct evidence presented by the re-submission, for every 100 patients treated with palbociclib plus letrozole in comparison with letrozole alone there would be:

- Approximately 8 more patients progression-free at 12 months based on PALOMA-1, Blinded Independent Central Review.
- Approximately 10 more patients at 12 months and 14 more patients at 24 months progression-free based on PALOMA-2, Blinded Independent Central Review.
- No improvement in OS, based on PALOMA-1.
- Approximately 54 additional patients would experience a grade ≥ 3 adverse event.
- Approximately 54 additional patients would experience grade 3 neutropenia (low count of one type of white blood cell, neutrophils, which carries an increased risk of infection) and 8 additional patients would experience grade 4 neutropenia.
- Approximately 2 additional patients would experience febrile neutropenia (development of fever in a patient with neutropenia).
- Approximately 42 additional patients would experience leukopenia (low white blood cell count).
- Approximately 15 additional patients would experience fatigue.
- The increased risk of pulmonary embolism (where an artery in the lungs becomes blocked by a blood clot) was small but observed in both clinical trials.

Interpretation of the clinical evidence

6.20 The re-submission described palbociclib plus letrozole as superior in terms of comparative effectiveness and worse but manageable in terms of comparative safety over letrozole (or anastrozole) alone.

6.21 The safety claim is changed from the previous submission which claimed palbociclib plus letrozole to be “slightly worse but manageable” in terms of comparative safety.

6.22 The following issues regarding the efficacy claim were raised in the evaluation and by ESC:

- The benefit of palbociclib in delaying progression, and hence time to next therapy, remains uncertain given the context of other available therapies for advanced breast cancer including well-tolerated oral therapies. The pre-PBAC response provided embargoed information on the Ibrance Real World Insights (IRIS, ClinicalTrials.gov Identifier: NCT03159195), and claimed the PFS and OS results were similar to those for the PALOMA studies.

- In PALOMA 1 the difference in OS, although in favour of palbociclib (median increase of 3.0 months, and 3.4/100 additional patients alive at 36 months), remained not statistically significant (p=0.28). The PSCR (p1) stated that at the time of the updated analysis of OS, the median duration of follow-up was 64.7 months (95% CI, 58.8, 73.0) and the OS benefit may have been confounded by subsequent therapies. The ESC noted that PALOMA-1 was not designed or powered to detect differences in OS.
- 6.23 The ESC considered that the re-submission’s clinical claim for the comparative safety was appropriate. Higher rates of adverse events were observed with palbociclib plus letrozole compared to letrozole alone in PALOMA-1 and PALOMA-2, although in general these events could be managed by experienced clinicians. The ESC further noted that adverse events with first line palbociclib plus letrozole would likely be worse than adverse events with currently available treatments used as later line treatment.
- 6.24 The claim that palbociclib plus letrozole vs. letrozole alone maintained quality of life in both studies was not adequately supported. While there were no statistically significant differences between the treatment arms in PALOMA-2 in the FACT-B, FACT-G and EQ-5D results, PALOMA-2 was not powered to detect changes in patient reported outcomes. The pre-PBAC response argued that it is important to consider the reduced quality of life with progression, and the 10 month (difference in median PFS) delay in progression when palbociclib is added to an NSAI. The pre-PBAC response further argued that the next treatment for patients who progress on a NSAI is likely everolimus plus exemestane, a combination that can be associated with stomatitis, rash, fatigue and diarrhoea.
- 6.25 For context, the PBAC recalled its previous considerations of treatment of HER2-positive breast cancer. As an example, the PBAC noted the incremental benefits in OS were statistically significant for pertuzumab + trastuzumab + docetaxel vs trastuzumab + docetaxel, at two different data cut-offs (May 2012 and February 2014, considered at the March 2014 and November 2014 meetings). The magnitude of the difference was larger than observed with palbociclib in PALOMA 1 (Table below).

Table 8: Benefits summary of pertuzumab (CLEOPATRA) and trastuzumab (M77001)

Outcome	N	HRR or RR (95%CI)	Median months (95% CI)		Increment
			Pertuzumab + trastuzumab + docetaxel	Trastuzumab + docetaxel	
Benefits					
PFS (median months, 95% CI) (May 2012 cut-off)	808	0.69 (0.58, 0.81)	18.7 (17, 22)	12.4 (10, 14)	6.3
OS (median months, 95% CI) (May 2012 cut-off)	808	0.66 (0.52, 0.84)	Not reached (42, -)	37.6 (34, -)	N/A
OS (median months, 95% CI) (Feb 2014 cut-off)	808	0.68 (0.56, 0.84)	56.5	40.8	15.7

Source: Adapted from November 2014 Public Summary Document for item 7.5.

- 6.26 Overall, in the absence of a demonstrated gained in OS or quality of life, the ESC

considered the benefits of palbociclib to be uncertain, and in this context noted the UpToDate article by Hayes et al (last updated in August 2017), titled Systemic treatment for metastatic breast cancer: General principles, which states:

- The primary goals of systemic treatment for metastatic breast cancer are prolongation of survival, alleviation of symptoms, and maintenance or improvement in quality of life, despite toxicity associated with treatment.
- The optimal measure of therapeutic efficacy is debated. OS is the gold standard for comparing therapies, but it requires prolonged follow-up and may be diluted by the effects of subsequent treatment. However, no other endpoint, including progression-free survival, time to tumour progression, or objective response rate, has been shown to be a good surrogate for OS.

6.27 The pre-PBAC response presented an article entitled ‘Treatment approach to metastatic hormone receptor positive, HER2-negative breast cancer: Endocrine therapy’ (UpToDate, Ma and Dickler, October 2017), which states that the goal of therapy is to “choose the therapy that is most likely to stabilize or reduce the burden of disease with the fewest side effects and maintain that therapy until either unacceptable toxicities are evident or disease progression occurs”. Furthermore, UpToDate, Ma and Dickler, states “Given the consistent benefits observed with CDK inhibitors and AI, we prefer those regimens in the front-line setting”. The response also presented the opinion from three oncologists including ‘While improvements in progression free survival are not always followed by improvements in overall survival that generally applies to treatments that produce only modest improvements on existing standard care. Palbociclib has however had a profound effect on progression free survival not offset by significant toxicity, since a good quality of life is maintained and lasts a lot longer than the control arms.’

Economic analysis

6.28 The re-submission presented a cost-effectiveness and cost-utility analysis. This is unchanged from the previous submission.

6.29 A summary of the model structure is presented in the table below. Key changes in the model from the previous submission are described below.

Table 9: Summary of model structure and rationale

Component	Summary
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Outcomes	Deaths, LYG and QALYs
Time horizon	130 cycles (9.97 years) in the model base case versus a maximum of 82 months in the PALOMA-1 trial and 33 months in the PALOMA-2 trial. The length of follow-up changed from the previous submission (maximum of 44 months in the PALOMA-1 trial). Previously, the PBAC considered that 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

Component	Summary
	and paclitaxel, 2008). (PSD, March 2017, item 7.13). The results are highly sensitive to the time horizon, with the current approach favouring palbociclib.
Methods used to generate results	A (partitioned-survival) Markov model
Health states	1) alive pre-progression, 2) alive post-progression. 3) death
Utilities	<p>EQ-5D (UK tariff) from PALOMA-2 (February 2016): Pre-progression, palbociclib + letrozole = 0.736 Pre-progression, letrozole alone= 0.712 Note: Mixed effects model.</p> <p>Decrement for post-progression (-0.272) based on Lloyd (2006) (UK general population, hypothetical scenarios, standard gamble, n=100): Post-progression, palbociclib + letrozole = 0.464 Post-progression, letrozole alone= 0.440</p> <p>The approach is changed from the previous submission, which applied utility estimates based on Lloyd (2006). The difference in utility between the palbociclib+letrozole and letrozole arms (which applies both pre- and post-progression) is larger than was assumed in the previous submission.</p> <p>The re-submission does not justify why patients treated with palbociclib plus letrozole would continue to have a utility increment post-progression, after treatment has ceased.</p>
Cycle length	28 days
Transition probabilities	PFS and OS were estimated using only fitted parametric (log-logistic) functions for the entire time horizon. The parametric functions were fitted to the Kaplan-Meier estimates for investigator-assessed PFS in PALOMA-2 and updated OS in PALOMA-1. This is changed from the previous submission, which applied Kaplan-Meier estimates for PFS and OS in PALOMA-1 until cycle 39 and then extrapolated using a log-logistic function until cycle 130.
Costs	<p><u>Drug costs</u></p> <ul style="list-style-type: none"> • Dosage of palbociclib was based on median dose and mean relative dose intensity (RDI) of palbociclib in PALOMA-2. The mean RDI decreased compared to the previous submission. • Dosage of letrozole was based on median dose in PALOMA-2. 100% RDI assumed. The cost of letrozole was excluded in the previous submission. • Duration of treatment with palbociclib and letrozole was based on median investigator-assessed PFS in PALOMA-2. The model continues to apply drug costs to only those patients in the pre-progression state and then assumes no use of palbociclib + letrozole beyond 27 cycles. • Use of granulocyte colony-stimulating factors (G-CSF) was based on usage in PALOMA-2. Cost of G-CSF was based on the PBS cost of filgrastim, assuming 5 mcg/kg/day and 70 kg. The use of G-CSF increased compared to the previous submission. <p><u>Other costs</u></p> <p>Disease costs – annual pre-progression costs: \$ [redacted] pa. Disease costs – annual post-progression costs: \$ [redacted] pa. One-off event costs – non-fatal progression: \$ [redacted] One-off event costs – death: \$ [redacted]</p> <p>These costs were changed compared to the previous submission. There were multiple issues with the methodology used to estimate disease costs and one-off event costs.</p>

Source: Compiled during the evaluation

6.30 A summary of the key drivers of the model is presented in the table below. The method of applying trial data in the model and source of utilities are new key drivers of the model.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Truncation of drug costs	Drug costs truncated at 27 cycles.	High, favours palbociclib
Time horizon	10 years	Moderate, favours palbociclib
Method of applying trial data applied in model	Estimated PFS and OS using only fitted parametric (log-logistic) functions for the entire time horizon (rather than applying Kaplan-Meier trial data until median follow-up)	Moderate, favours palbociclib
Extrapolation of OS	Applied log-logistic function (rather than Weibull)	Moderate, favours palbociclib
OS gain	OS from PALOMA-1 (not statistically significant).	Moderate, favours palbociclib
Source of PFS	Investigator assessed PFS (rather than BICR assessed PFS).	Unknown, likely favours palbociclib
Utility advantage for palbociclib both pre- and post-progression	Utility advantage maintained throughout the model	Moderate, favours palbociclib

Source: Compiled during the evaluation.

6.31 The results of the economic evaluation for this re-submission and from the March 2017 submission are presented in the table below.

Table 11: Results of the stepped economic evaluation

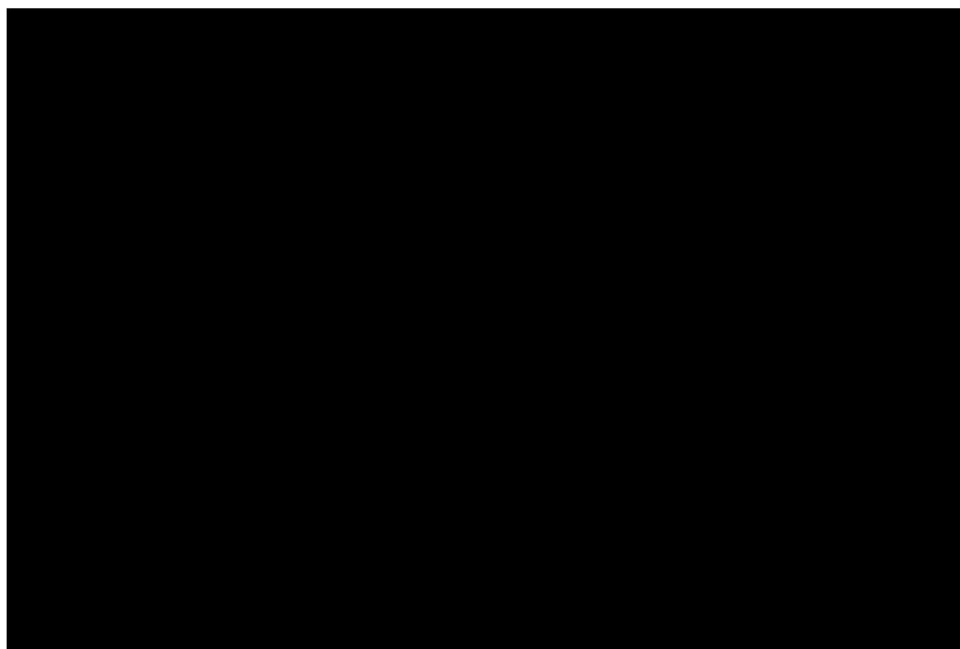
Step and component	Palbociclib group (palbociclib + letrozole)	Usual care group (letrozole alone)	Increment
Step 0: trial-based costs and outcomes (time horizon = 70 cycles, or median duration of follow-up in PALOMA-1 (December 2016) = 64.7 months)			
Costs	████████	████████	████████
Years of life lived	3.033	2.854	0.179
Incremental cost/extra years of life gained			████████
Step 1: modelled evaluation (time horizon = 10 years or 130 cycles)			
Costs	████████	████████	████████
Years of life lived	3.535	3.271	0.265
Incremental cost/extra year of life gained			████████
Step 2: modelled evaluation (time horizon = 10 years, incorporating utilities)			
Costs	████████	████████	████████
QALYs	2.349	1.938	0.411
Incremental cost/extra QALYs gained			████████
March 2017 submission			
Step 2: trial evidence translated to clinical outcomes, the Australian population/setting, extrapolated, with additional modelling and transformed into an economic outcome			
Costs	████████	████████	████████
QALYs	2.420	1.897	0.523
Incremental cost/extra QALYs gained – March 2017 submission			████████

^a Added during the evaluation

Source: D.5.2 and D.5.3, p233 of the re-submission and D.5.2 and D.5.3, p205 of the previous submission.

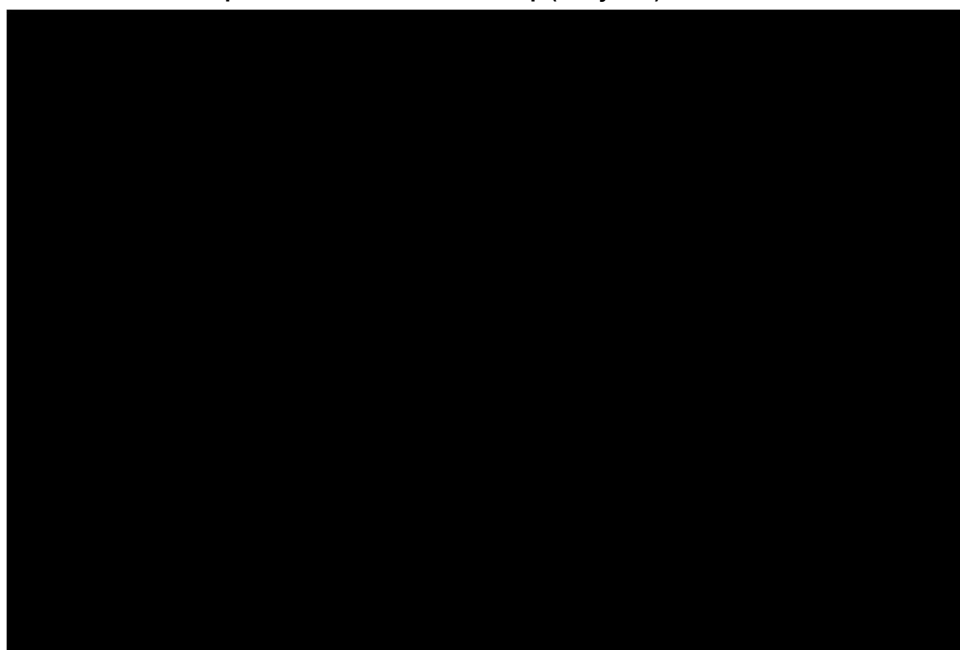
6.32 Figure 6 and Figure 7 compare the estimates of PFS and OS generated by the model to the PFS and OS Kaplan-Meier curves from the trials. The re-submission estimated PFS and OS using the fitted parametric functions for the entire time horizon. At the March 2017 meeting, the PBAC considered that extrapolating from the point of median follow-up would be appropriate (PSD, March 2016, item 7.13). Sensitivity analysis indicates the results for the current model are sensitive to the approach used to model PFS and OS.

Figure 6: PFS estimated in the re-submission's economic model versus PFS when based on Kaplan-Meier data from PALOMA-2 and extrapolated from median follow-up (25 cycles)



Source: Extracted from Palbociclib Section D – 28Jun2017.xls of the re-submission.

Figure 7: OS estimated in the re-submission's economic model versus OS when based on Kaplan-Meier data from PALOMA-1 and extrapolated from median follow-up (70 cycles)



Source: Extracted from Palbociclib Section D – 28Jun2017.xls of the re-submission.

6.33 The PSCR (p2) stated the resubmission used the PFS results from PALOMA-2 to inform the economic model based on the PBAC's advice when reviewing the March 2017 submission. The PSCR argued that extrapolating the KM curves from two data sources (PALOMA-1 and PALOMA-2) required use of the fitted parametric functions that do not rely on empirical step changes in survival curves to inform the transition probabilities to avoid, for example, cycles in the model where the probability of death is greater than the probability of progression. The ESC did not consider this argument was strong enough to justify use of the parametric functions from day 1. Figure 8 shows the effect on the cost /QALY when changing the year in the model at which the extrapolation replaces the KM curves for both OS and PFS. The re-submission uses point 0 (Day 1). The ESC noted that the approach in the re-submission favoured palbociclib because the overall trend demonstrated in the figure was that the cost/QALY increased the later the time point at which the extrapolation replaces the Kaplan-Meier curve. The pre-PBAC response argued that the use of the fitted parametric functions from day 1 is both appropriate and necessary, so that empirical step changes in survival curves based on the observed sample size are not used to erroneously inform transition probabilities.

Figure 8: The point (the year in the model) at which the extrapolation replaces the KM curves in the economic model



The redacted figure shows ICERs in the range of \$45,000/QALY - \$105,000/QALY

6.34 The treatment effect was assumed to persist for the model duration. This evaluation stated that this is not appropriate, especially as the median duration in PALOMA-2 (used to estimate PFS) was 22.3 – 23.0 months, compared to a model time horizon of 10 years, and OS in PALOMA-1 was not statistically significant. Previously, the PBAC

considered that this assumption is inappropriate (PSD, March 2017, item 7.13). The PSCR (p2) stated there is no evidence to suggest that the treatment effect will not persist for the model duration. The ESC acknowledged there is no evidence, but questioned the biological plausibility of this assumption.

6.35 The re-submission presented univariate sensitivity analysis. The key results are presented in the table below.

Table 12: Results of univariate sensitivity analyses

Univariate analyses	Incremental costs	Incremental effectiveness (QALYs)	Incremental cost-effectiveness (\$/QALY)
Base case	██████	0.411	██████
Use of K-M data from PALOMA trials up to maximum follow-up in the trials	██████	0.338	██████
Utilities: as per Peasgood et al. (2010)	██████	0.287	██████ Should be ██████ ^a
Utilities: Same utility post-progression (average across treatment arms)	██████	0.383	██████
Time horizon = 5 years (65 cycles)	██████	0.306	██████
Time horizon = 7.5 years (98 cycles)	██████	0.376	██████
Weibull extrapolation OS only – from cycle 1	██████	0.358	██████
Weibull extrapolation OS only – from cycle 71	██████	0.337	██████
Removing truncation of drug costs beyond 27 cycles	██████	0.411	██████

^a Based on Palbociclib – Section D 28Jun2017.xlsx

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

The redacted table shows ICERs in the range of \$45,000/QALY - \$200,000/QALY

6.36 The re-submission increased the maximum duration of treatment with palbociclib + letrozole (20.2 months (22 cycles) to 24.8 months (27 cycles), while reducing dose intensity (94.1% to 86.8%) to reflect the PALOMA-2 data.

6.37 The model applied drug costs in the pre-progression state only and assumed no use of palbociclib + letrozole beyond 27 cycles, despite a large proportion of patients being progression free beyond cycle 27. The assumption of no drug use beyond 27 cycles underestimated the average drug cost per patient. Without this assumption the incremental costs increased from \$██████ to \$██████ per patient, and thus the ICER increased to \$105,000/QALY - \$200,000/QALY gained. The PSCR (p1) stated that the assumed duration of palbociclib use was based on time from randomisation to progression rather than the time from randomisation to treatment cessation. The PSCR argued the discrepancy in median PFS and time to treatment cessation reflects the fact that some cease treatment for reasons other than disease progression and that this would be expected to occur in practice, as it did in the trials. The ESC noted the point, but considered that the effect of truncation at 27 cycles on underestimating duration of treatment was likely to be larger than the effect of using PFS as a proxy for time to discontinuation in overestimating treatment duration. The ESC further noted the impact on the ICER of truncating treatment costs is large and the corrected ICER is likely to be closer to \$105,000/QALY - \$200,000/QALY gained

than \$45,000/QALY - \$75,000/QALY. Data on the time to discontinuation [REDACTED], would likely provide some clarity regarding the actual drug use in the trial. The pre-PBAC response maintained that use of median PFS (24.8 months) is conservative, because it over-estimates duration of treatment and that assuming all subjects stay on treatment until progression is unrealistic, and the contention that it over-estimates duration of treatment to a lesser extent than median PFS underestimates duration of treatment is speculative. The PBAC noted the sponsor had not addressed the key issue regarding the calculation of drug costs in the model and that no costs were included beyond cycle 27.

- 6.38 The model was sensitive to the approach used to estimate the gain in OS. Some of this was due to the high level of uncertainty in the clinical trial results – the OS gain in PALOMA-1 was small (3.0 months), the difference was not statistically significant (P=0.28), and the confidence intervals for the hazard ratio were wide.
- 6.39 The cost/QALY is sensitive to the choice of the log-logistic function over the Weibull function to extrapolate survival. The log-logistic and Weibull functions had similar AICs and BICs, with the log-logistic having a slightly lower AIC and BIC. Extrapolation of OS using a Weibull function from cycle 1 increased the ICER from a base case of \$45,000 - \$75,000 to \$45,000 - \$75,000 per QALY gained. Extrapolation of OS and PFS using a Weibull function from cycle 1, as noted in the PSCR (p2) decreased the ICER from a base case of \$45,000 - \$75,000 to \$45,000 - \$75,000 per QALY gained.
- 6.40 Sensitivity analyses on the shape and scale parameters describing the parametric functions were not conducted by the re-submission. These sensitivity analyses were unable to be conducted during the evaluation as the re-submission did not report the upper and lower 95% confidence intervals and no output logs were provided.
- 6.41 The model was sensitive to the 10 year time horizon. At the March 2017 consideration, the PBAC noted the claimed survival rate of approximately 10% at 10-years in hormone receptor positive (HR+), HER2-negative (HER2-) advanced breast cancer, but considered a shorter time horizon was appropriate given the immaturity of the existing OS data and that any increase in OS was uncertain. 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 PSCR (p2) noted the OS results from PALOMA-1, with a maximum observed follow-up of 6.9 years, showed that 15.8% of palbociclib patients remained alive and hence considered reference to a three-year time horizon not relevant. The PSCR presented a sensitivity analysis based on a shorter time horizon of 7.5 years (a time point noted to have minimal extrapolation) and this resulted in a \$/QALY of \$45,000 - \$75,000. The ESC noted that the ICER is sensitive to the time horizon, although agreed with the PSCR that a 3 year time horizon was too short to adequately capture the benefits and costs of treatment. The ESC considered that a shorter time horizon was appropriate given the immaturity of the existing OS data and that any increase in OS was uncertain based on the available data.
- 6.42 The model was sensitive to the source of utility estimates. The previous submission applied utility estimates based on Lloyd (2006) whereas the re-submission used pre-

progression values derived from the EQ-5D (UK tariff) from PALOMA-2. Although use of the trial data was considered appropriate, the ESC noted that the difference in utility values between the palbociclib+letrozole and letrozole arms (both pre- and post-progression) was larger (0.024) than was assumed in the previous submission (0.005). The ESC considered that the difference in the utilities pre-progression may not be plausible given there were no statistically significant differences in the patient report outcomes between the treatment arms in PALOMA-2. The ESC considered the difference in utilities by treatment post-progression was not justified as treatment had ceased, and continued effect on quality of life beyond discontinuation was unlikely. When the same utility value was applied post-progression (the average across treatment arms), the ICER increased from a base case of \$45,000 - \$75,000 to \$45,000 - \$75,000 per QALY gained. The pre-PBAC response argued that the sensitivity analysis undertaken by the ESC resulted in an ICER that increased by only a small amount (approximately 7%), which is generally within cost-effective thresholds for innovative oncology products.

- 6.43 The impact of using the investigator-assessed PFS, rather than the BICR PFS, is unknown due to the lack of a formal sensitivity analysis conducted by the re-submission using the BICR PFS.
- 6.44 Overall, the ESC considered that the base case cost/QALY in the re-submission was underestimated. In addition to the issue of truncating treatment costs, the ESC noted that a number of other issues raised in this advice each had a small impact on the ICER/QALY, however the collective impact was unknown.

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

- 6.45 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 receives 26 packs) (based on median PFS in PALOMA-2).
- 6.46 This differs from the drug costs for palbociclib (undiscounted) in the base case economic model of \$ [REDACTED] per patient. The difference is largely due to the truncation of drug costs at 27 cycles in the economic model.

Estimated PBS usage & financial implications

- 6.47 This submission was not considered by the Drug Utilisation Sub-Committee (DUSC).
- 6.48 The re-submission used an epidemiological (incidence based) approach to estimate the utilisation and financial implications associated with the requested PBS listing of palbociclib in combination with a NSAI (letrozole or anastrozole) as initial endocrine-based therapy in postmenopausal women with HR+, HER2- ABC. This is unchanged from the previous submission, except for the inclusion of males and grandfathered patients, and the incidence of recurrence and HR+/HER2- breast cancer was based on DUSC advice on the March 2017 submission. A sensitivity analysis of the financial implications of the proposed PBS-listing using the patient estimates derived through a market share approach was also presented. The DUSC has previously noted that

the market share approach was limited by a lack of accurate cancer stage data and that use of the epidemiological approach for the base case was appropriate.

- 6.49 In order to address the DUSC's concerns regarding the previous submission, the re-submission:
- Included a note in the PBS restriction that patients whose disease progressed on palbociclib would no longer be eligible for PBS-subsidised palbociclib.
 - Added grandfathered patients in the financial estimates.
 - The ESC noted that estimate of patient numbers appropriately included males with breast cancer.
- 6.50 The PBAC previously considered that there was a likelihood that average treatment duration with palbociclib will be longer than the estimate from PALOMA-2 (median PFS of 24.8 months), and that there is a risk of treatment with palbociclib continuing post-progression even with a restriction specifying conditions relating to ceasing treatment (PSD, March 2017, item 7.14). In regards to the risk of treatment with palbociclib continuing post-progression, the PSCR (p3) presented responses from three oncologists to argue that it is not likely that patients would be treated beyond progression. The ESC considered that there is now more clinic experience using CDK4/6 inhibitors and agreed with the PSCR.
- 6.51 The ESC reiterated the previous view of the PBAC that there was the potential for use outside the proposed restriction in patients being treated with letrozole or anastrozole at the time of palbociclib's listing (i.e. the prevalent pool of patients).
- 6.52 The ESC noted that the proposed PBS restriction is narrower than the TGA indication, which does not mention a patient's menopause status and does include in combination with fulvestrant in patients who have received prior therapy. The ESC considered given current clinical practice that these differences would not result in significant use outside the restriction.
- 6.53 The re-submission estimated that if the combination of palbociclib and a NSAID is listed on the PBS, the expected uptake would be 42.5% in the first year and 85% for the four subsequent years. The ESC considered that given the community's interest in this oral treatment that the estimate of uptake, particularly in year 1 was underestimated.
- 6.54 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 of the re-submission. The financial estimates below exclude the costs of G-CSF as they are not PBS listed for this indication. However, the cost of G-CSFs would potentially be incurred by hospital budgets. The PSCR (p3) discussed that prophylactic G-CSF support is not required and G-CSF is rarely required for resolution [of neutropenia]; there is no recommendation to prescribe G-CSF in the product information, which states alternate ways to deal with neutropenia, such as dose reduction. The sponsor stated that PBAC may wish to consider whether the current PBS streamlined authority restrictions for filgrastim

should be expanded to capture rare, unresolved occurrences of CDK4/6 inhibitor-induced high grade neutropenia.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of patients treated with palbociclib	█	█	█	█	█
Number of scripts dispensed of palbociclib ^a	█	█	█	█	█
Estimated financial implications of palbociclib + NSAID (\$)					
Cost to PBS/RPBS	█	█	█	█	█
Copayments	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█
Estimated financial implications for endocrine therapies (\$)					
Cost to PBS/RPBS	█	█	█	█	█
Copayments	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█
Net financial implications (\$)					
Net cost to PBS/RPBS (including filgrastim)	█	█	█	█	█
Net cost to PBS/RPBS (excluding G-CSF)	█	█	█	█	█
Net cost to MBS	█	█	█	█	█
March 2017 submission					
Number of patients treated	█	█	█	█	█
Estimated financial implications of palbociclib + NSAID, cost to PBS/RPBS less copayments (\$)	█	█	█	█	█
Net cost to PBS/RPBS (\$)	█	█	█	█	█
Net cost to MBS (\$)	█	█	█	█	█

a. Assuming 26 per course as estimated by the re-submission.

Source: Table E.2.6, p281, Table E.2.4 p280, Table E.2.10-11 p284-5, Table E.3.4, p288 and Table E.4.1, p289 of the re-submission, and Table E.2.5, Table E.2.6 p252 and Table E.2.10 p255 and Table E.2.11, p256 of the previous submission

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year the net cost to the PBS would be more than \$100 million per year.

6.55 The total net financial cost for the PBS/RPBS was estimated to be more than \$100 million over 5 years. This is changed from the previous submission, which estimated the total net financial cost for the PBS/RPBS to be more than \$100 million over 5 years, largely due to the reduced proposed effective DPMQ for palbociclib.

6.56 There is potential for the net cost to the PBS to be greater than the estimate in the re-submission due to higher than expected uptake and the potential for use in patients being treated with letrozole or anastrozole (i.e. the prevalent pool of patients) at the time of palbociclib's listing. On the other hand, there is potential for the net cost to the PBS to be less than the estimate in the re-submission as:

- G-CSFs are not PBS listed for the treatment of selective CDK4/6 inhibitor induced neutropenia (though the sponsor has raised the possibility of a PBS listing), and
- Uptake may be shared between palbociclib and ribociclib if ribociclib, a near-

market comparator, is also concurrently PBS-listed. The ESC noted that if one or both agents were listed for the same patient population, the total financial cost would be similar, as long as patients only accessed one agent until progression.

- 6.57 Overall, the ESC considered that there is potential for the net cost to the PBS to be greater than the estimate in the re-submission.

Quality use of medicines

- 6.58 The re-submission proposed to provide education to healthcare professionals (especially oncologists and nurses) and conduct post-marketing surveillance. This is unchanged from the previous submission.

Financial management – risk sharing arrangements

- 6.59 The re-submission acknowledged that a volume-based risk sharing arrangement may be required and may reduce the financial uncertainty. No further details were provided.

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 non pre-menopausal patients with hormone receptor positive (HR+), HER2-negative (HER2-) locally advanced inoperable breast cancer and metastatic breast cancer on the basis of high and uncertain cost-effectiveness, and uncertainties regarding the magnitude of incremental benefit of palbociclib. Additionally, the PBAC was of the view that the likely net cost to the PBS of listing palbociclib would be more than \$100 million over the first five years, and as such, there would be a significant opportunity cost to the Commonwealth, despite the reduced price proposed for palbociclib in the re-submission.
- 7.2 The PBAC noted the consumer comments and acknowledged there is significant public interest in the listing of palbociclib. The PBAC noted the commonly reported benefits of palbociclib included improved quality of life, and delayed disease progression and time to chemotherapy, but it had a very high financial cost to patients without PBS subsidy.
- 7.3 The PBAC maintained its position 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.
- 7.4 The PBAC noted since consideration of the original submission, palbociclib has been TGA registered for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy; or in combination with fulvestrant in patients who have received prior therapy.

- 7.5 The PBAC noted that most of the concerns raised with the proposed restriction in March 2017 were addressed with the current proposed restriction. The PBAC recalled its previous advice that it may be appropriate to identify a subgroup of the patient population who would gain most benefit in order to justify the approach used to estimate the cost-effectiveness, at the price proposed by the sponsor. The sponsor argued in the re-submission that it was not possible to identify such a subgroup and access to palbociclib for the intent-to-treat (ITT) patient population as defined in the trials was clinically warranted.
- 7.6 In regards to subsidy of palbociclib for patients who are treated with a NSAID at the time of PBS-listing (a prevalent pool of patients), the PBAC reiterated that, while it may be reasonable to expect that the addition of palbociclib may provide a clinical benefit, 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. However, the PBAC noted that palbociclib use may extend to this group of patients and consequently increase the total cost to government.
- 7.7 The PBAC considered, if both listed on the PBS, that ribociclib and palbociclib should have similar restriction criteria given they belong to the same class of drug and are registered for similar indications. The PBAC recommended that any points of difference, such as clinical criteria for access, would need to be clearly justified and defined.
- 7.8 The PBAC considered that the nominated main comparator, a NSAID (letrozole or anastrozole) alone, remained appropriate. The PBAC agreed with ESC that ribociclib, which was also considered by the Committee for a similar indication at its November 2017 meeting, should have been considered as a near market comparator.
- 7.9 The PBAC noted the re-submission was based on the same two head-to-head RCTs comparing palbociclib + letrozole to letrozole alone (PALOMA-1, n= 165 and PALOMA-2, n= 666) as presented in the original submission. The PBAC noted additional follow-up data were available for PALOMA-1 but not PALOMA-2. The PBAC recalled the ESC's concerns regarding the PALOMA-1 trial design and the associated significant risk of bias. 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 reiterated that data from PALOMA-2 would be more informative in evaluating the comparative efficacy and safety of palbociclib.
- 7.10 The PBAC noted that both trials showed statistically significant improvements in PFS. These results are unchanged from the previous submission. The PBAC recalled 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.
- 7.11 The PBAC noted that with the additional follow-up for PALOMA-1, OS remained not statistically significantly different, though was numerically different in favour of palbociclib. Further, the PBAC noted that the magnitude of the difference was reduced with the additional data (median increase in OS of 3.0 vs 4.2 months; HR

0.8970 (95% CI 0.623, 1.294) vs 0.813 (95% CI 0.492, 1.345)). The re-submission did not provide updated OS results from PALOMA-2. The PBAC recalled from its previous consideration that results will be available in 2020 and retained the view that further outcome data from PALOMA-2, particularly relating to OS, would be informative.

- 7.12 The re-submission claimed that palbociclib plus letrozole had superior comparative effectiveness to letrozole (or anastrozole) and a worse but manageable safety profile. The PBAC noted the increased PFS reported in the trials, but maintained its previous position that the overall comparative clinical benefit of palbociclib remained unclear in the absence of evidence of a survival benefit and limited clinical trial evidence of patient-reported improvements in their quality of life, and given the data indicating increased adverse events.
- 7.13 The PBAC recalled its previous concern that across the two trials, high rates of patients experienced neutropenia, and a higher number of patients experienced troublesome symptoms such as fatigue. The PBAC noted the updated safety results from PALOMA-1 were consistent with those presented in the March 2017 submission. The PBAC considered that the claim of inferior comparative safety was consistent with the data and that some of the impact of adverse events had appropriately been applied in the economic modelling.
- 7.14 The PBAC noted that the re-submission's economic model had directly addressed some of the Committee's previous concerns. The PBAC noted compared with the March 2017 submission that both the cost and benefits were reduced and the resulting ICER was similar \$45,000/QALY - \$75,000/QALY vs \$ - \$45,000/QALY - \$75,000/QALY /QALY). However, the PBAC considered a number of concerns regarding the economic model remained and as such, the revised base case cost/QALY in the re-submission was substantially underestimated. The concerns included:
- Drug costs being excluded beyond cycle 27 in the model. The model applied drug costs to patients in the pre-progression state only and assumed no use of palbociclib + letrozole beyond 27 cycles, despite a large proportion of patients being progression free. This resulted in the drug costs being substantially underestimated. The PBAC noted if drug costs are applied in the model based on PFS the ICER increased to \$105,000/QALY - \$200,000/QALY.
 - The model time horizon. The time horizon of 10 years was unchanged from the previous submission, where the PBAC considered this assumption to be too long given the available clinical evidence. The PBAC noted that the OS results from PALOMA-1 had a maximum observed follow-up of 6.9 years and showed that 15.8% of palbociclib patients remained alive, however the PBAC reiterated its view that 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.
 - Use of investigator-assessed rather than centrally PFS. The PBAC reiterated its view that that the BICR assessed PFS of PALOMA-2 was more appropriate data to inform the base case model.
 - Inclusion of an OS gain while the available clinical evidence does not

demonstrate statistically significant difference in OS. However, the PBAC noted the economic model resulted in a health benefit of 0.332 life years (LY, undiscounted) and 0.265 LY (with 5% discounting) which is similar to the difference of 3.0 months in median OS from the updated PALOMA-1 data.

- Use of the fitted parametric functions for PFS and OS for the entire model time horizon. Acknowledging that the data for PFS and OS are derived from different trials, the PBAC reiterated its preference for extrapolating from the point of median follow-up.
- Use of a log-logistic extrapolation function and assuming that the treatment effect persists for the model duration. The PBAC noted the model was moderately sensitive to the parametric function selected for the extrapolation of OS. The PBAC maintained that assuming a treatment benefit for the model duration is inappropriate based on the available evidence.
- The difference in the post-progression utility values for the palbociclib+letrozole and letrozole arms. The PBAC agreed with ESC that the difference in utilities by treatment post-progression was not justified as treatment had ceased, and continued effect on quality of life beyond discontinuation was unlikely.

7.15 The PBAC noted that the total net financial cost for the PBS/RPBS was estimated to be more than \$100 million over 5 years. Noting the arguments raised in the re-submission, the PBAC reiterated its concern that usage and financial impact remained likely to be underestimated, due to:

- The likelihood that the average treatment duration with palbociclib will be longer than the estimate from PALOMA-2.
- Some risk of treatment with palbociclib continuing post-progression even with a restriction specifying conditions relating to ceasing treatment and noting the view of clinical experts in re-submission.
- 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), which would be outside the propose listing.
- 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 the estimated 500 patients. The pre-PBAC response indicated that the sponsor had included more than 250 advanced breast cancer patients in clinical trials of palbociclib and is currently recruiting up to 300 patients in clinical trials of palbociclib for other forms of breast cancer. The PBAC were uncertain which of these patients would be eligible for treatment with the proposed restriction.
- Underestimated uptake of palbociclib in the eligible population in the first year of listing. The PBAC agreed with ESC that given the community's interest in this oral treatment that the estimate of uptake was underestimated.

7.16 The PBAC noted that there was significant opportunity cost of listing palbociclib, particularly in the context of the uncertain cost-effectiveness. The PBAC reiterated, as acknowledged by the sponsor, that some of these uncertainties could be managed in a risk-share agreement between the Commonwealth and the sponsor.

7.17 The PBAC considered a re-submission should include:

- A revised restriction excluding patients treated with a NSAID at the time of listing palbociclib.
- Revisions to the economic model to address the concerns noted in paragraph 7.14.
- A reduced price for palbociclib to achieve a base case ICER of \$45,000/QALY - \$75,000/QALY.
- Revised financial forecasts that include a risk share agreement that appropriately limits the financial risk to the Commonwealth.

7.18 The PBAC recalled that it previously 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. The PBAC noted that palbociclib is registered for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with fulvestrant in patients who have received prior therapy. The PBAC considered that there may be a clinical place for a listing of palbociclib and fulvestrant for the second line treatment of patients. The PBAC noted that cost-effectiveness of fulvestrant has not been considered by the PBAC.

7.19 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 is committed to working with the PBAC and the Department of Health to make palbociclib available for the treatment of locally advanced and metastatic HR-positive, HER2-negative breast cancer.