

7.17 PALBOCICLIB

Capsules, 75 mg, 100 mg, 125 mg Ibrance[®], Pfizer Australia Pty Ltd

1 Purpose of Application

1.1 The minor submission requested an authority required listing for palbociclib for treatment of non-premenopausal patients with HR+/HER2- locally advanced inoperable breast cancer and metastatic breast cancer. Major submissions for this listing were considered and rejected by the PBAC at its March 2017 and November 2017 meetings. The key differences from the November 2017 resubmission are:

- A further price reduction was proposed, reducing the effective DPMQ of palbociclib 21 x 75 mg, 100 mg or 125 mg capsules from \$ [REDACTED] to \$ [REDACTED].
- With a model horizon of 10 years and drug costs applied beyond 27 cycles, the reduced palbociclib price resulted in a cost/QALY gained of \$105,000/QALY - \$200,000/QALY compared with \$105,000/QALY - \$200,000/QALY in the November 2017 submission.
- Alternative approaches to calculation of treatment costs in the economic model were presented.
- The reduced palbociclib price resulted in a net cost to the PBS/RPBS of more than \$100 million over 5 years compared with more than \$100 million over 5 years in the November 2017 submission.
- A risk-share agreement, [REDACTED]

2 Requested listing

2.1 The submission requested the following new listing. The requested listing is the same restriction that was proposed in the November 2017 PBAC submission [November 2017 PBAC Meeting, Public Summary Document (PSD) pg1-4].

2.2 Suggestions and additions proposed by the Secretariat to the requested listing as per the November 2017 resubmission are in italics and suggested deletions are crossed out with strikethrough.

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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
Treatment phase:	Initial treatment
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 not be receiving PBS-subsidised treatment with letrozole or anastrozole at the time of application</i> 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

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Prescriber Instructions	<p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug</p> <p>Authority applications for initial treatment must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed [TBA] - PBS Supporting Information Form which includes: (i) a copy of the pathology reports from an Approved Pathology Authority confirming the presence of hormone receptor and lack of presence of HER2 gene amplification by in situ hybridisation (ISH); and (ii) a copy of the signed patient acknowledgement form.</p>
Administrative Advice	<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>
Note	<p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug</p>

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:	Locally advanced or metastatic
Condition:	Breast cancer
PBS Indication:	Locally advanced or metastatic breast cancer
Treatment phase:	Continuing treatment

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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:	<i>Patient must have previously received PBS-subsidised treatment with this drug for this condition</i> AND 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 <i>The condition must be human epidermal growth factor receptor 2 (HER2) negative,</i> AND <i>The condition must be inoperable</i> AND <i>Patient must have a WHO performance status of 0 to 2</i> AND <i>Patient must not be receiving PBS-subsidised letrozole or anastrozole</i> AND <i>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)</i>
Population criteria:	<i>Patient must not be pre-menopausal</i>
Prescriber Instructions	<i>Endocrine-based therapy is the first-line treatment for postmenopausal women with hormone receptor positive breast cancer recommended by current treatment guidelines.</i> <i>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug</i> <i>Authority applications for continuing treatment must be made in writing and must include:</i> <i>(a) a completed authority prescription form; and</i> <i>(b) a completed [TBA] - PBS Supporting Information Form which includes:</i> <i>(i) a copy of the signed patient acknowledgement form.</i>

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Administrative Advice	<p><i>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:</i></p> <p><i>Complete response (CR) is disappearance of all target lesions.</i></p> <p><i>Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.</i></p> <p><i>Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.</i></p> <p><i>Stable disease (SD) is small changes that do not meet above criteria.</i></p> <p><i>No applications for increased maximum quantities will be authorised.</i></p> <p><i>No applications for increased repeats will be authorised.</i></p> <p><i>Special Pricing Arrangements apply.</i></p> <p><i>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).</i></p> <p><i>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</i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i></p> <p><i>Department of Human Services</i></p> <p><i>Complex Drugs</i></p> <p><i>Reply Paid 9826</i></p> <p><i>HOBART TAS 7001</i></p>
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- 2.3 The November 2017 resubmission requested that the PBAC consider whether patients who are currently well managed with a NSAI (letrozole or anastrozole) should also be able to access the addition of palbociclib to their NSAI regimen at the time of PBS listing (a prevalent pool of patients). The PBAC considered that any resubmission should include a revised restriction excluding patients treated with a NSAI at the time of listing palbociclib [November 2017 PBAC Meeting, PSD paragraph 7.17]. The PBAC reaffirmed this view and advised that the wording of the treatment criteria for the initial restriction should specify that patients must have had no prior systemic endocrine-based therapy for this indication.
- 2.4 The PBAC reiterated that if both ribociclib and palbociclib were listed on the PBS, they should have the same restriction criteria given they belong to the same class of drug and are registered for similar indications.
- 2.5 The PBAC advised that both initial and continuing restrictions should be authority required (telephone).
- 2.6 The sponsor requested in the November 2017 resubmission that patients who are being treated with palbociclib prior to PBS-listing be grandfathered to receive PBS-subsidised treatment with this drug. The November 2017 resubmission stated that ■■■ patients would likely be eligible for grandfathering in year 1. The resubmission did not provide proposed text for a grandfather restriction. 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. PBAC indicated that grandfathered patients should be the same as the PBS population and not a wider population. This means that grandfathered patients should be included in the subsidisation cap provided they would have met the PBS criteria at the time they commenced treatment with palbociclib. The same grandfathering criteria would apply to ribociclib if it was recommended for listing on the PBS.

- 2.7 The requested restriction is considered to be complex.

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

3 Background

- 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.


- 3.2 Palbociclib was initially considered by the PBAC for initial endocrine-based therapy indication at the March 2017 meeting and rejected on the basis that the PBAC did not know the circumstances in which palbociclib would be registered for use in Australia by the TGA at the time of its consideration of the submission. The PBAC noted that single agent endocrine therapy as first-line therapy is associated with significant clinical benefits in most patients and the addition of palbociclib increases the toxicity of treatment with an uncertain effect on overall survival. It was uncertain which patients would most benefit from the addition of palbociclib to a first line 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) [March 2017 PBAC Meeting, PSD paragraph 7.1].

- 3.3 A major resubmission for palbociclib was considered by the PBAC at the November 2017 meeting and rejected 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 resubmission.

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

Table 1: PBAC matters of concern in previous consideration (November 2017)

Matters of concern	How the resubmission addresses it
<p><u>Comparator</u> 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.</p>	<p>An indirect comparison of palbociclib and ribociclib and calculation of equi-effective doses was provided with the minor resubmission.</p>
<p><u>Clinical evidence</u> 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 and reiterated that data from PALOMA-2 would be more informative in evaluating the comparative efficacy and safety of palbociclib.</p> <p>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)).</p>	<p>A Pfizer-sponsored abstract of a post-hoc analysis of the PALOMA-2 trial based on more than 3 years follow-up was provided. This abstract reports an increased median PFS for palbociclib of 27.6 months [95% CI: 22.4, 30.3], 2.8 months more than the median PFS reported in the final analysis presented in the November 2017 resubmission. The median PFS for letrozole alone is unchanged.</p> <p>Cost-effectiveness and financial estimates have not been updated to reflect this post-hoc evidence.</p> <p>Not addressed. OS results from PALOMA-2 are expected in 2020.</p>
<p><u>Economic model</u> 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 - \$200,000 per QALY gained.</p> <p><u>Additional model concerns</u></p> <ul style="list-style-type: none"> • The time horizon of 10 years was unchanged from the previous (March 2017) submission, where the PBAC considered this assumption to be too long given the available clinical evidence. • Use of investigator-assessed rather than centrally assessed PFS. • Inclusion of an OS gain while the available clinical evidence does not demonstrate statistically significant difference in OS. • 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 	<p>Two alternative approaches to calculation of treatment costs are proposed:</p> <ul style="list-style-type: none"> - Applying drug costs to match progression (treatment duration) as suggested in the PBAC minutes results in an ICER of \$105,000 - \$200,000 or \$105,000 - \$200,000 with the revised DPMQ. - Applying drug costs up to median PFS for all patients regardless of when they progressed (no drug costs beyond 27 cycles) results in an ICER of \$45,000-\$75,000 with the revised DPMQ. <p>Not addressed.</p>

<p>trials, the PBAC reiterated its preference for extrapolating from the point of median follow-up.</p> <ul style="list-style-type: none"> • Use of a log-logistic extrapolation function and assuming that the treatment effect persists for the model duration. • 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. 	
<p>Financial estimates Usage and financial impact remain likely to be underestimated due to: longer treatment duration, continuing palbociclib post-progression, use in patients being treated with letrozole or anastrozole at the time of listing, the number of grandfathered patients, and underestimated uptake.</p> <p>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.</p>	<p>Not addressed.</p> <p>RSA proposed </p>

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

4 Comparator

- 4.1 The previous major submissions considered by the PBAC in March 2017 and November 2017 nominated the comparator as a NSAI (letrozole or anastrozole) alone. This is unchanged from the previous submissions. The PBAC previously considered that this is the appropriate comparator.
- 4.2 At the November meeting the PBAC considered that it would be appropriate to consider ribociclib as a near market comparator. Ribociclib was also considered at the November 2017 and March 2018 PBAC meetings. In the minor resubmission the sponsor provided a comparison and equi-effective doses for palbociclib and ribociclib.

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

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted that no consumer comments were received for this item.

5.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the palbociclib submission, on the basis of PFS benefit. The PBAC noted that MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for palbociclib as 3 compared to letrozole alone. MOGA noted that the score may increase to 4 when OS data matures (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).¹

Clinical trials

5.4 The March 2017 submission and November 2017 resubmission were 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.

5.5 As a minor submission, no new clinical trials were presented in the resubmission. An abstract presenting an updated post-hoc analysis of PFS in PALOMA-2 was provided, though the updated results were not used in the modelled cost effectiveness and financial estimates. As a minor submission, the additional data presented have not been evaluated.

5.6 Details of the trials presented are provided in the table below.

Table 2: 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	2017 ASCO Meeting, J Clin Oncol 35, 2017 (suppl; abstr 1001)

¹ Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 26:1547-73, 2015

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Trial ID/First Author	Protocol title/ Publication title	Publication citation
	letrozole (L) vs letrozole alone for frontline treatment of ER+/HER2–advanced breast cancer (PALOMA-1; TRIO-18).	
	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 CTCR-AACR San Antonio Breast Cancer Symposium. United States. 77 (4 Supplement 1) (no pagination), 2017. Date of 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)
	Rugo, H., Finn, R., Dieras, V. et al. Palbociclib Plus Letrozole as First-Line Therapy in Estrogen Receptor-positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Efficacy and Safety Updates With Longer Follow-Up Across Patient Subgroups.	Presented at the 40th Annual San Antonio Breast Cancer Symposium (SABCS); December 5–9, 2017; San Antonio, TX, USA

Source: Table B.2.2 p31 of the November 2017 re-submission.

Comparative effectiveness

5.7 The trial results for palbociclib as presented in Table 3 remain unchanged from the November 2017 major submission.

Table 3: 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
Investigator (31 May 2017)	NR	NR	27.6 (22.4, 30.3)	14.5 (12.3, 17.1)	NR	HR 0.56 (0.46, 0.69) 1-sided p-value <0.000001
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: PBAC Ratified minutes November 2017, Table 5 p13.

5.8 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.

- 5.9 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), was not statistically significant ($p=0.28$). The sponsor has previously suggested that the OS may be confounded by subsequent treatments. PALOMA-1 was not designed or powered to detect differences in OS. The PBAC noted that if there is no survival gain for patients treated with palbociclib, then gains in PFS would appear to be at the expense of reduced post-progression survival.
- 5.10 The updated post hoc-analysis of PALOMA-2 is based on data with a median follow-up of approximately 37 months, compared with a median follow-up of approximately 23 months for the data presented in the November 2017 resubmission. Results from the post-hoc analysis demonstrated a median investigator assessed PFS of 27.6 months [95% CI: 22.4, 30.3] for patients treated with palbociclib + letrozole compared with 14.5 months [95% CI: 12.3, 17.1] for letrozole alone (HR=0.56 [95% CI: 0.46, 0.69]). The minor submission noted that the increased PFS for palbociclib may mean that patients require an additional 2 packs of palbociclib and corresponding letrozole.
- 5.11 The indirect comparison for palbociclib and ribociclib identified:
- A number of exchangeability limitations resulting from baseline differences between trials, as identified by ESC in relation to the July 2017 ribociclib submission (item 6.18 ribociclib PSD, July 2017 PBAC Meeting). The pre-PBAC response noted that compared with the ribociclib MONALEESA-2 trial, patients recruited into PALOMA-2 tended to have more aggressive disease (e.g. shorter disease-free interval and more metastatic sites), could have co-morbid cardiac disease or cardiac dysfunction and could continue to receive concomitant medications that prolong QT interval.
 - An unadjusted indirect comparison of PFS gave a HR of [redacted] [95% CI: [redacted], [redacted]] for palbociclib versus ribociclib. The submission nominated a non-inferiority margin of 1.4 based on a published value for early breast cancer (Tanaka et al 2012)² as no studies specific to advanced breast cancer were identified. Based on this, non-inferiority failed to be demonstrated. A matched adjusted indirect comparison was also provided, to adjust for patient and trial characteristics (visceral disease, proportion of bone only, number of metastatic sites, disease-free interval, previous neo/adjuvant chemo/endocrine therapy, hormone receptor status, ECOG performance status, previous metastatic treatment, age and race). The matched adjusted indirect comparison gave a HR of [redacted] [95%CI: [redacted], [redacted]] for PFS. As a minor submission the indirect comparison and its interpretation were not evaluated. Results of the indirect comparison are shown in Table 4.

² Tanaka S, Kinjo Y, Kataoka Y et al. Statistical issues and recommendations for non-inferiority trials in oncology: a systematic review. Clin Cancer Res; 18(7); 1837-47.

Table 4: Results from Unadjusted and Matched Adjusted Indirect Comparisons

Outcome	Unadjusted Indirect Comparison	Matched Adjusted Indirect Comparison
PFS (HR; 95% C.I.)	██████████	██████████
CBR (OR; 95% C.I.)	██████████	██████████
ORR (OR; 95% C.I.)	██████████	██████████

Source: Technical report MAIC analyses, HR hazard ratio, a: ██████████

Comparative harms

- 5.12 In PALOMA-1 and PALOMA-2, more patients treated with palbociclib + letrozole were reported to have AEs compared with those treated with letrozole alone.
- 5.13 Safety outcomes reported in the indirect comparison indicated similar event rates for common adverse events such as neutropenia and fatigue and slightly lower grade 3/4 adverse event rates for palbociclib compared with ribociclib. There were fewer dose reductions and dose interruptions for palbociclib compared with ribociclib. Adverse event rates and dose reduction rates were not adjusted for the longer duration of treatment and follow-up in the PALOMA-2 trial (median 19.8 months duration of treatment for palbociclib and median 23.0 months duration of follow-up) compared with the MONALEESA-2 trial (median 13 months duration of treatment for ribociclib and approximately 15.3 months duration of follow-up).

Clinical claim

- 5.14 The November 2017 resubmission 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. This is unchanged in the minor resubmission.
- 5.15 In relation to the November 2017 resubmission the PBAC "...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." [November 2017 PBAC Meeting, PSD paragraph 7.12]. The PBAC reiterated its view that the magnitude of long term benefit is unknown and noted without a gain in OS, the gain in PFS would be at the expense of reduced post-progression survival.
- 5.16 The PBAC previously 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 [November 2017 PBAC Meeting, PSD paragraph 7.13].
- 5.17 The resubmission proposed the following clinical claim based on the indirect comparison for palbociclib versus ribociclib:

- Palbociclib is non-inferior to ribociclib in terms of efficacy.
 - Palbociclib has non-inferior safety compared with ribociclib.
- 5.18 The PBAC noted an indirect comparison of ribociclib and palbociclib was also considered at the November 2017 meeting based on information included in the ribociclib submission (ribociclib PSD, November 2017 PBAC Meeting).
- 5.19 Overall, the PBAC noted that there is limited data to support the clinical claim for palbociclib compared with ribociclib but considered that the claim of non-inferior efficacy and safety appears reasonable.

Economic analysis

- 5.20 In the major resubmission considered by the PBAC in November 2017, a cost-effectiveness and cost-utility analysis against letrozole alone was presented. The minor resubmission did not alter the economic model structure from November 2017 but sought to respecify the best estimate of the base case ICER by reducing the price of palbociclib.
- 5.21 Additionally, the minor resubmission presented two alternative methods of calculating drug costs. The previous base case cost-effectiveness ratios and the updated cost-effectiveness ratios are shown in the table below.
- 5.22 In the November 2017 resubmission 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 (referred to in the minor resubmission as Method A). This assumption underestimated the average drug cost per patient and the impact on the ICER of truncating treatment costs is substantial.
- 5.23 The minor resubmission presented the model results with drug costs applied based on the time to progression (referred to as Method B).
- The minor resubmission presented a third, alternative approach to calculation of drug costs in the model (referred to as Method C). This method applies drug costs up to the median PFS (cycle 27) for all patients, including patients who progress prior to cycle 27.

Table 4: Updated cost-effectiveness ratios

Method	Original DPMQ	ICER based on original DPMQ	Revised DPMQ	ICER based on revised DPMQ
Base case for March 2017 PBAC meeting* (Method A)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Base case for November 2017 meeting (Method A)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Drug costs match progression (Method B)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Drug costs applied for median PFS for all patients (Method C)	N/A	N/A	\$ [REDACTED]	\$ [REDACTED]

* The base case November 2016 economic model was based on PFS and OS from PALOMA-1.

Source: Palbociclib minor submission Table 1, p 4.

- 5.24 When drug costs are applied in the model beyond 27 cycles, based on PFS (referred to as Method B) the ICER increases to \$105,000 - \$200,000 per QALY gained compared with the base case of \$45,000 - \$75,000 per QALY gained using the proposed price in the November 2017 resubmission. With the revised DPMQ of \$ [REDACTED] proposed in the minor resubmission this method of calculating treatment costs results in an ICER of 105,000 - \$200,000 per QALY gained. The respecified base case ICERs were verified by the Department.
- 5.25 The PBAC reiterated that drug costs should be based on PFS (Method B). The PBAC noted the sponsor's arguments in the pre-PBAC response regarding Method B but considered that the other approaches to calculation of drug costs were not justified and would substantially underestimate the costs.
- 5.26 In addition to truncating drug costs for palbociclib at cycle 27, a number of outstanding concerns were previously raised regarding the economic model as outlined in Table 1.

Economic analysis – cost minimisation versus ribociclib

- 5.27 Assuming non-inferiority of efficacy and safety between ribociclib and palbociclib, the sponsor proposed that the same relative dose intensity (RDI) should be applied to both (or that the RDI does not need to be considered) and therefore the equi-effective doses are palbociclib 125 mg and ribociclib 600 mg per day for 21 days of a 28 day cycle. The sponsor stated a comparison of dose reductions and dose interruptions suggests that palbociclib may be better tolerated than ribociclib.
- 5.28 The PBAC recalled that the equi-effective doses for palbociclib and ribociclib proposed in the ribociclib November 2017 resubmission were adjusted for RDI (ribociclib November 2017 PBAC meeting, PSD paragraphs 6.48-6.50).
- 5.29 The PBAC considered the doses as used in the trials, including RDI adjustments, should be used as a basis for the equi-effective doses. The PBAC considered deviating from the actual doses used the trials had not been adequately justified.

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

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

- 5.30 Assuming a cost of \$ [REDACTED] per pack, one pack is used per 28 days, with no dose reduction the cost/patient/year is \$ [REDACTED]. If a dose reduction of [REDACTED] % (from PALOMA-2) is applied the drug cost/patient/year is \$ [REDACTED].
- 5.31 Assuming the patient is treated for 24.8 months (based on median PFS in PALOMA-2, 26 February 2016 data cut-off) the drug cost/patient/course is \$ [REDACTED] or with adjustment for RDI is \$ [REDACTED].
- 5.32 This is lower than the drug cost/patient/course in the model using Method B (drug costs match progression), which is \$ [REDACTED] (undiscounted; RDI adjusted); and higher than the drug cost/patient/course using Method C (drug costs applied up to cycle 27 for all patients regardless of progression) which is \$ [REDACTED] (undiscounted; RDI adjusted).

Estimated PBS usage & financial implications

- 5.33 The minor submission estimated a net cost to the PBS/RPBS of more than \$100 million in Year 5 of listing, with a total net cost to the PBS/RPBS of more than \$100 million over the first 5 years of listing. This is summarised in the table below as well as the expected patient/prescription numbers (palbociclib minor submission). The estimated cost to the PBS for palbociclib is reduced by \$30 – 60 million over the first 5 years of listing due to the reduced DPMQ. The PBAC noted that the opportunity cost of listing palbociclib at the proposed DPMQ remains high.
- 5.34 At the November 2017 meeting the PBAC was concerned that usage and financial impact remained likely to be underestimated. Some key factors included:
- the average treatment duration for palbociclib is assumed to be the median progression-free survival observed in the palbociclib+letrozole arm of the PALOMA-2 trial (i.e. 755 days). The PBAC previously considered that the time on palbociclib in practice is likely to be longer;
 - there is a risk of treatment with palbociclib continuing post-progression even with a restriction specifying conditions relating to ceasing treatment; and
 - uptake estimates in year 1 are expected to be higher based on community interest in accessing oral therapy.
- 5.35 The PBAC noted that the updated PFS from the December 2017 publication provided with the minor resubmission suggests that PFS may be longer and therefore treatment duration may be longer than that assumed in the financial estimates.
- 5.36 The financial estimates model presented in the minor resubmission apply the full number of scripts per year to the estimated number of treated patients. This

overestimates the number of prescriptions as not all patients will be fully compliant to treatment. The March 2017 submission for palbociclib reported a median relative dose intensity of 93% in the palbociclib plus letrozole arm of the PALOMA-2 trial (PALOMA 2 Clinical Study Report: 12.1.1, Table 35). DUSC (March 2015) considered that this assumption was a likely overestimate.

- 5.37 Although uptake was potentially underestimated in year 1, it is likely that uptake was overestimated in the out years of the forward estimates period.

Table 5: Net cost of drug to government

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	2017	2018	2019	2020	2021	2022
Estimated extent of use						
Eligible and suitable patients	████	████	████	████	████	████
Treatment uptake assumption ^a	43%	85%	85%	85%	85%	85%
Number of patients initiating treatment ^b	████	████	████	████	████	████
Number of prescriptions dispensed (PBS/RPBS) ^c	████	████	████	████	████	████
Estimated financial implications of palbociclib – March 2018 Minor (DPMQ \$████)						
Cost to PBS/RPBS	████	████	████	████	████	████
Copayments	████	████	████	████	████	████
Overall cost to PBS/RPBS less copayments	████	████	████	████	████	████
Estimated financial implications for tamoxifen, letrozole, anastrozole, and exemestane (+/- everolimus)						
Cost to PBS/RPBS	████	████	████	████	████	████
Copayments	████	████	████	████	████	████
Cost to PBS/RPBS less copayments	████	████	████	████	████	████
Estimated total cost to PBS/RPBS (all drugs)	████	████	████	████	████	████
Estimated financial implications of palbociclib – November 2017 resubmission						
Cost to PBS/RPBS	████	████	████	████	████	████
Copayments	████	████	████	████	████	████
Cost to PBS/RPBS less copayments	████	████	████	████	████	████
Estimated financial implications for tamoxifen, letrozole, anastrozole, and exemestane (+/- everolimus)						
Cost to PBS/RPBS	████	████	████	████	████	████
Copayments	████	████	████	████	████	████

- adequately addressed through a reduction in price in conjunction with financial caps.
- 6.2 The PBAC acknowledged the previously expressed significant public interest in the listing of palbociclib and noted that the Medical Oncology Group of Australia (MOGA) expressed its strong support for the palbociclib submission, on the basis of PFS benefit.
 - 6.3 The PBAC considered that the nominated main comparator, a NSAI (i.e. letrozole or anastrozole) alone, remained appropriate. The PBAC considered that ribociclib was an appropriate near market comparator, and noted ribociclib was also considered by the Committee for a similar indication at its March 2018 meeting.
 - 6.4 The PBAC noted the minor resubmission 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 previous submissions. The PBAC noted that the February 2017 cut-off post hoc analysis provided with the minor resubmission demonstrated a longer median investigator assessed PFS for patients treated with palbociclib + letrozole of 27.6 months compared with 24.8 months, and that the increase in PFS for palbociclib may mean that patients require, on average, an additional 2 packs of palbociclib and corresponding letrozole.
 - 6.5 The PBAC recalled that OS data from PALOMA-2 is not yet mature and noted that 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), was not statistically significant (p=0.28). Based on the available data, the PBAC considered that if there was no overall survival gain then the gains in progression free survival for patients treated with palbociclib are likely to be at the expense of reduced post-progression survival. The PBAC considered that the claim of superior comparative effectiveness over an NSAI alone was adequately supported on the basis of the improvement in progression free survival. However, the overall magnitude of long term clinical benefit from the addition of palbociclib is highly uncertain.
 - 6.6 The PBAC recalled that it had previously considered the claim of inferior safety compared with a NSAI alone to be reasonable. The inferior safety profile could impact on the quality of life in the progression-free state.
 - 6.7 The PBAC noted the indirect comparison of palbociclib and ribociclib presented in the minor resubmission and recalled the comparison presented in the November 2017 ribociclib resubmission. The PBAC noted that there are limited data to support the clinical claim for palbociclib compared with ribociclib but considered that the claim of non-inferior clinical effectiveness and safety appears reasonable.
 - 6.8 The PBAC noted the economic model presented in the minor resubmission was the same as that considered at the November 2017 meeting except that three approaches for calculating the drug costs were presented. The PBAC considered calculating the drug costs based on the modelled PFS (Method B) was appropriate

and the alternative methods (A and C) were not adequately supported and underestimated the drug costs.

- 6.9 The PBAC noted the outstanding issues with the model as outlined in Table 1, however considered that the estimated quality adjusted life years gained (0.411) were not inconsistent with the available clinical trial data for palbociclib (██████████). The PBAC noted that the estimated life years gained (0.265) generated by the model were modest and not inconsistent with the numerical increase in OS observed in the trial, however the PBAC considered this gain was highly uncertain given the overall survival difference in the trial was not statistically significant.
- 6.10 The PBAC considered the ICER using Method B to calculate drug costs of \$105,000 - \$200,000 per QALY gained to be unacceptably high. The PBAC considered that an ICER of \$15,000 - \$45,000 per QALY gained is required for palbociclib to be considered cost-effective. This ICER reflects the current uncertainty regarding the long-term benefits of palbociclib in terms of overall survival gain and the large opportunity cost of listing at a higher ICER. The PBAC further noted that with a substantially reduced price for palbociclib the assumed overall survival gain for palbociclib is no longer a model driver as the costs associated with delaying progression offset a substantial proportion of the drug costs. The PBAC considered it appropriate for the model to not rely on an overall survival gain for an acceptable ICER to be achieved. The PBAC considered the cost-effectiveness could be adequately addressed through a reduction in price in conjunction with financial caps.
- 6.11 The PBAC noted the minor resubmission proposed that the equi-effective doses for palbociclib and ribociclib should be based on the recommended doses without adjustment for the relative dose intensity as reported in the clinical trials. The PBAC further noted that this was in contrast to the November 2017 ribociclib resubmission which proposed equi-effective doses be adjusted based on RDIs to reflect actual use in the clinical trials. The PBAC considered the doses as used in the trials, including RDI adjustments, should be used as a basis for the equi-effective doses. The PBAC considered deviating from the actual doses used in the trials had not been adequately justified. On this basis the equi-effective doses would be palbociclib ██████████ mg (██████████ mg x mean RDI of ██████████%) and ribociclib ██████████ per day for 21 days of a 28 day cycle.
- 6.12 The minor resubmission used an incidence-based approach to determine the patient numbers (considered reasonable by PBAC) and estimated a total of ██████████ packs of palbociclib would be dispensed over 5 years. This resulted in a total net cost to the PBS/RPBS of more than \$100 million. The PBAC noted the sponsor proposed a risk share arrangement ██████████.
- 6.13 The PBAC recalled its concerns from the November 2017 meeting that usage may be underestimated, but also noted that the assumption of 100% compliance and high

uptake rates in years 2 to 5 may have resulted in an overestimate of use. In addition the PBAC noted that as some patients will commence therapy partway through the year the number of scripts per patient in Year 1 is overestimated.

- 6.14 The PBAC noted that with the price that results in an ICER of \$15,000 - \$45,000 per QALY gained, the estimated net PBS/RPBS cost based on the estimated number of prescriptions in Table 5 (██████ over 5 years) would be more than \$100 million over the first 5 years (from \$10 - \$20 million in year 1, up to \$30 - \$60 million in year 5) and considered that the financial cap should not exceed this. The PBAC noted that the financial caps should be distributed proportionally to uptake rates noting that there would be a lower Cap in year 1 than later years. The Committee noted that should the currently near market product ribociclib be listed on the PBS before palbociclib is able to proceed to listing, palbociclib should join any listing and RSA arrangements that may be applied for ribociclib.
- 6.15 The PBAC advised that both initial and continuing restrictions should be authority required (telephone).
- 6.16 The PBAC advised the initial restriction should specify that patients should not have previously been treated with anastrozole or letrozole for this indication.
- 6.17 The PBAC also advised that the listing for palbociclib should include patients with an ECOG performance status of 0 to 2 and should exclude patients that develop disease progression whilst on treatment with ribociclib.
- 6.18 The PBAC considered that a grandfather restriction was appropriate, although patients should not be required to have accessed palbociclib only through the sponsor's access program in order to be eligible for grandfathering. The PBAC also recommended that only patients who met the PBS initiation criteria at the time they initiated treatment with palbociclib should be grandfathered to the PBS. That is that grandfathered patients should be the same as the PBS population and not a wider population. The PBAC noted that the sponsor requested a grandfather restriction, however did not propose a restriction. The PBAC considered that where grandfathering is requested, the sponsor should propose an associated restriction.
- 6.19 The PBAC recommended that if the currently near market product ribociclib and palbociclib are both listed on the PBS, the listing of palbociclib should be amended to state that palbociclib and ribociclib are not to be used in combination, and that patients should only be treated with either palbociclib or ribociclib, unless the patient develops an intolerance of a severity necessitating permanent treatment withdrawal. These amendments are outlined in the flow-on changes to listing in Section 7.
- 6.20 The PBAC noted that final overall survival results from the PALOMA-2 trial are expected to be available in 2020 and advised that if listed, the sponsor should provide these results to the PBAC.

- 6.21 The PBAC advised that palbociclib should be treated as interchangeable on an individual patient basis with ribociclib.
- 6.22 The PBAC advised that palbociclib is not suitable for prescribing by nurse practitioners.
- 6.23 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
PALBOCICLIB Capsule 75 mg, 100 mg, 125 mg	21	5	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:	Locally advanced or metastatic
Condition:	Breast cancer
PBS Indication:	Locally advanced or metastatic breast cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	The treatment must be in combination with anastrozole or letrozole.

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Clinical criteria:	Patient must not have previously been treated with an aromatase inhibitor AND The condition must be hormone receptor positive. AND The condition must be human epidermal growth factor receptor 2 (HER2) negative. AND The condition must be inoperable AND Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less.
Population criteria:	Patient must not be premenopausal.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

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:	Locally advanced or metastatic
Condition:	Breast cancer
PBS Indication:	Locally advanced or metastatic breast cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	The treatment must be in combination with anastrozole or letrozole.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not develop disease progression whilst being treated with this drug for this condition. AND Patient must have stable or responding disease
Population criteria:	Patient must not be premenopausal.
Prescriber Instructions	A patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

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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:	Locally advanced or metastatic
Condition:	breast cancer
PBS Indication:	Locally advanced or metastatic breast cancer
Treatment phase:	Initial – grandfather restriction
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	The treatment must be in combination with anastrozole or letrozole.
Clinical criteria:	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [listing date] AND Patient must not have previously been treated with an aromatase inhibitor prior to initiating treatment with this drug for this condition AND The condition must be hormone receptor positive; AND The condition must be human epidermal growth factor receptor 2 (HER2) negative; AND The condition must be inoperable AND Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2 prior to initiating treatment with this drug for this condition AND Patient must not have developed disease progression whilst being treated with this drug for this condition. AND Patient must have stable or responding disease
Population criteria:	The patient must not be premenopausal
Prescriber Instructions	A patient may qualify for PBS-subsidised treatment under this restriction once only.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

7.2 Flow-on changes to listing. The listing of palbociclib should be amended as follows should the currently near market product ribociclib be listed on the PBS prior to palbociclib. The changes are highlighted in italics and strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
PALBOCICLIB Capsule 75 mg, 100 mg, 125 mg	21	5	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:	Locally advanced or metastatic
Condition:	Breast cancer
PBS Indication:	Locally advanced or metastatic breast cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	The treatment must be in combination with anastrozole or letrozole. AND <i>The treatment must not be in combination with ribociclib</i>
Clinical criteria:	Patient must not have previously been treated with an aromatase inhibitor AND <i>Patient must not have previously been treated with ribociclib</i> OR <i>Patient must have developed an intolerance to ribociclib of a severity necessitating permanent treatment withdrawal</i> AND The condition must be hormone receptor positive. AND The condition must be human epidermal growth factor receptor 2 (HER2) negative. AND The condition must be inoperable AND Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less.
Population criteria:	Patient must not be premenopausal.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.
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

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Episodicity:	
Severity:	Locally advanced or metastatic
Condition:	Breast cancer
PBS Indication:	Locally advanced or metastatic breast cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	The treatment must be in combination with anastrozole or letrozole. <i>AND</i> <i>The treatment must not be in combination with ribociclib</i>
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition <i>AND</i> Patient must not develop disease progression whilst being treated with this drug for this condition. <i>AND</i> Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)
Population criteria:	Patient must not be premenopausal.
Prescriber Instructions	A patient who has progressive disease when treated with this drug for this condition is no longer eligible for PBS-subsidised treatment with this drug.
Administrative Advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.
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:	Locally advanced or metastatic
Condition:	breast cancer
PBS Indication:	Locally advanced or metastatic breast cancer
Treatment phase:	Initial – grandfather restriction
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	The treatment must be in combination with anastrozole or letrozole. <i>AND</i> <i>The treatment must not be in combination with ribociclib</i>

Clinical criteria:	<p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [listing date] AND Patient must not have previously been treated with an aromatase inhibitor prior to initiating treatment with this drug for this condition AND <i>Patient must not have previously been treated with ribociclib</i> OR <i>Patient must have developed an intolerance to ribociclib of a severity necessitating permanent treatment withdrawal</i> AND The condition must be hormone receptor positive; AND The condition must be human epidermal growth factor receptor 2 (HER2) negative; AND The condition must be inoperable AND Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2 prior to initiating treatment with this drug for this condition AND Patient must not have developed disease progression whilst being treated with this drug for this condition. AND Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)</p>
Population criteria:	The patient must not be premenopausal
Prescriber Instructions	A patient may qualify for PBS-subsidised treatment under this restriction once only.
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.</p>

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 has no comment.