

## 5.01 ABEMACICLIB, Tablet 50 mg, 100 mg and 150 mg, Verzenio<sup>®</sup>, Eli Lilly Australia Pty Ltd

### 1 Purpose of Application

- 1.1 Authority Required listing for abemaciclib as initial endocrine-based treatment for non-premenopausal patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer. Abemaciclib has not been considered by PBAC previously.
- 1.2 The submission presented a cost-minimisation analysis (CMA) versus ribociclib.

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

Component	Description
Population	Non-premenopausal patients with HR+/HER2- advanced breast cancer
Intervention	Abemaciclib, 150 mg twice daily (recommended dose), in combination with NSAI, until disease progression or unacceptable toxicity
Comparator	Ribociclib, 600 mg once daily (recommended dose) on days 1-21 of a 28 day cycle, in combination with NSAI, until disease progression, unacceptable toxicity or death.
Outcomes	Effectiveness: progression-free survival (PFS); objective response rate (ORR), clinical benefit rate (CBR) Safety: adverse events (CTCAE Grade 3 or 4, serious) and dose reductions
Clinical claim	In non-premenopausal patients with HR+/HER2- advanced breast cancer, abemaciclib plus NSAI is clinically equivalent to ribociclib plus NSAI in terms of comparative effectiveness and safety

CBR: clinical benefit rate; CTCAE: Common Terminology Criteria for Adverse Events; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; NSAI: non-steroidal aromatase inhibitor; ORR: objective response rate; PFS: progression-free survival.  
Source: Table 1.1.1, p 21 of the submission.

### 2 Requested listing

- 2.1 The submission presented the key differences between the proposed restriction for abemaciclib and the current PBS restriction for ribociclib. The differences are highlighted in bold text below. In the submission, suggestions and additions were added in italics and strikethrough was used for deletions.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Dispensed price for maximum quantity	Proprietary Name	Manufacturer
ABEMACICLIB 150 mg tablet 100 mg tablet 50 mg tablet	1	56	5	\$ [redacted] [published] [redacted] [effective]	VERZENIO™	Eli Lilly Australia Pty Ltd

**Table 2: Initial treatment**

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:	N/A
Severity:	Locally advanced or metastatic
Condition:	Breast cancer

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<b>PBS Indication:</b>	Locally advanced or metastatic breast cancer
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	<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
<b>Treatment criteria:</b>	The treatment must be in combination with anastrozole or letrozole <b>AND</b> <b><i>The treatment must not be in combination with ribociclib</i></b>
<b>Clinical criteria:</b>	Patient must not have previously been treated with an aromatase inhibitor <b>for this indication</b> <b>AND</b> <b><i>Patient must not have previously been treated with ribociclib</i></b> <b>OR</b> <b><i>Patient must have developed an intolerance to ribociclib of a severity necessitating permanent treatment withdrawal</i></b> 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. AND <b>Patient must require dosage reduction requiring 100 mg tablet <sup>a</sup></b> <b>Patient must require dosage reduction requiring 50 mg tablet <sup>b</sup></b>
<b>Population criteria:</b>	Patient must not be premenopausal
<b>Cautions</b>	<del>QT monitoring is required for patients treated with this drug.</del>
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised

a Criterion only included in the restriction for 100 mg strength

b Criterion only included in the restriction for 50 mg strength

**Table 3: Continuing treatment**

<b>Category/ Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	N/A
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Breast cancer
<b>PBS Indication:</b>	Locally advanced or metastatic breast cancer
<b>Treatment phase:</b>	Continuing treatment

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<b>Restriction:</b>	<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
<b>Treatment criteria:</b>	The treatment must be in combination with anastrozole or letrozole <b>AND</b> <b>The treatment must not be in combination with ribociclib</b>
<b>Clinical criteria:</b>	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 <b>AND</b> <b>Patient must require dosage reduction requiring 100 mg tablet <sup>a</sup></b> <b>Patient must require dosage reduction requiring 50 mg tablet <sup>b</sup></b>
<b>Population criteria:</b>	Patient must not be premenopausal
<b>Prescriber Instructions</b>	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.
<b>Cautions</b>	<del>QT monitoring is required for patients treated with this drug.</del>
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised

a Criterion only included in the restriction for 100 mg strength

b Criterion only included in the restriction for 50 mg strength

**Table 4: Grandfathering treatment**

<b>Category/ Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	N/A
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Breast cancer
<b>PBS Indication:</b>	Locally advanced or metastatic breast cancer
<b>Treatment phase:</b>	Initial – grandfather restriction
<b>Restriction:</b>	<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
<b>Treatment criteria:</b>	The treatment must be in combination with anastrozole or letrozole <b>AND</b> <b>The treatment must not be in combination with ribociclib</b>

<b>Clinical criteria:</b>	<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  <b>AND</b>  <b>Patient must not have previously been treated with ribociclib</b>  <b>OR</b>  <b>Patient must have developed an intolerance to ribociclib of a severity necessitating permanent treatment withdrawal</b>  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  AND  Patient must not develop disease progression whilst being treated with this drug for this condition  AND  Patient must have stable or responding disease  <b>AND</b>  <b>Patient must require dosage reduction requiring 100 mg tablet <sup>a</sup></b>  <b>Patient must require dosage reduction requiring 50 mg tablet <sup>b</sup></b></p>
<b>Population criteria:</b>	Patient must not be premenopausal
<b>Prescriber Instructions</b>	A patient may qualify for PBS-subsidised treatment under this restriction once only
<b>Cautions</b>	<b><del>QT monitoring is required for patients treated with this drug.</del></b>
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised

a Criterion only included in the restriction for 100 mg strength (added during the evaluation)

b Criterion only included in the restriction for 50 mg strength (added during the evaluation)

Source: Table 1.4.2-1.4.4, pp35 of the submission.

- 2.2 The submission noted that only four patients continued to receive abemaciclib as of 28 August 2018 and that it is considered unlikely that these patients will require grandfathering to PBS-reimbursed treatment (p35 of the submission). The PBAC considered that the grandfathering restriction would not be required as these patients who are currently taking non-PBS subsidised abemaciclib would be eligible to access abemaciclib under the initial restriction.

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

### 3 Background

#### **Registration status**

- 3.1 **TGA status at time of PBAC consideration:** The submission was made under TGA/PBAC parallel process. Abemaciclib is currently under review by the TGA and Health Canada as a work-share arrangement, an initiative of the Australia-Canada-Singapore-Switzerland (ACSS) Consortium, with Health Canada leading the clinical section of the review. A Clinical Evaluation Report was not produced under the work-

share arrangement. Regulatory responses to Health Canada's assessment were provided with the Pre-Sub-Committee Response (PSCR). The TGA decision is expected in April 2019.

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

## **4 Population and disease**

4.1 In Australia, the age-standardised incidence rate for breast cancer is 124 per 100,000 females. It is estimated that 18,087 women and 148 men will be diagnosed with breast cancer in 2018 (AIHW 2017). HR+/HER2- is the most common type of breast cancer and accounts for about 70% of all cases, with about 30% eventually progressing to metastatic breast cancer. Metastatic breast cancer has an estimated overall survival (OS) of approximately three years.

4.2 Abemaciclib was proposed to be considered as an alternative cyclin D-dependent kinases (CDK) 4 and 6 inhibitor to ribociclib for use as initial endocrine-based treatment in non-premenopausal patients with HR+/HER2- advanced breast cancer.

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

## **5 Comparator**

5.1 The submission nominated ribociclib plus NSAID as the main comparator (p25 of the submission). The ESC considered this was appropriate.

5.2 The submission noted that palbociclib, another CDK 4 and 6 inhibitor, was recommended by the PBAC in March 2018 but has not progressed to PBS listing (p25 of the submission). The submission did not include a comparison with palbociclib.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

6.2 The PBAC noted and welcomed the input from an individual (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments noted that abemaciclib provides patients with an alternate option to other CDK 4/6 inhibitors because of its different side effect profile. This was emphasised in the input received from the Breast Cancer Network Australia (BCNA), which noted that abemaciclib is an option for patients with heart conditions, is less likely to cause neutropenia, and speculated that it may be beneficial for use in patients with brain metastasis. The BCNA also highlighted that the continuous dosing schedule (compared with three

weeks on, one week off schedule for ribociclib) of abemaciclib would be appealing to patients.

- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the abemaciclib submission on the basis of improved progression-free survival (PFS) based on the MONARCH-3 trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for abemaciclib plus aromatase inhibitor, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement), based on a comparison with an aromatase inhibitor alone. MOGA noted the ESMO-MCBS score may increase to 4 when overall survival (OS) data matures.

### Clinical trials

- 6.4 The submission was based on an indirect comparison of two randomized trials: MONARCH-3 comparing abemaciclib plus NSAI to placebo plus NSAI (anastrozole or letrozole) (n=493), and MONALEESA-2 comparing ribociclib plus letrozole to placebo plus letrozole (n=668).

- 6.5 Details of the trials presented in the submission are provided in Table 5.

**Table 5: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
MONARCH-3	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Nonsteroidal Aromatase Inhibitors (Anastrozole or Letrozole) plus LY2835219, a CDK4/6 Inhibitor, or Placebo in Postmenopausal Women with Hormone Receptor-Positive, HER2-Negative Locoregionally Recurrent or Metastatic Breast Cancer with No Prior Systemic Therapy in this Disease Setting. Clinical Study Report (CSR) Body: Data cut-off: 31 January 2017 CSR Synopsis: Data cut-off: 31 January 2017 CSR Addendum Body: Data cut-off: 03 November 2017	Report date: 18 July 2017 Report date: 13 July 2017 Report date: 01 February 2018
I3Y-MC-JPBM	CSR Addendum Synopsis: Data cut-off: 03 November 2017	Report date: 01 February 2018
NCT02246621	Protocol  Statistical Analysis Plan  Goetz MP, Toi M, Campone, M et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer.  Abstracts: Goetz et al., 2018 Goetz et al., 2015 Leo et al., 2018	Approved: 03 September 2014; Amendment (b) 16 December 2016 Approved 08 May 2015; V5 approved 14 April 2017. J Clin Oncol 2017; 35:3638-46
MONALEESA-2	Hortobagyi G.N, Stemmer S.M, Burris H.A. et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer.	New Engl J Med 2016; 375:1738-48
CLEE011A2301	Hortobagyi G.N, Stemmer S.M, Burris H.A. et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus	Ann Oncol 2018; 29:1541-7

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Trial ID	Protocol title/ Publication title	Publication citation
NCT01958021	<p>letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer.</p> <p>Janni W, Alba E, Bachelot T. et al. First-line ribociclib plus letrozole in postmenopausal women with HR+, HER2- advanced breast cancer: Tumor response and pain reduction in the phase 3 MONALEESA-2 trial.</p> <p>O'Shaughnessy J, Petrakova K, Sonke G.S, et al. Ribociclib plus letrozole versus letrozole alone in patients with de novo HR+, HER2- advanced breast cancer in the randomized MONALEESA-2 trial.</p> <p>Sonke G.S, Hart L.L, Campone M et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptor-positive, HER2-negative breast cancer in the randomized MONALEESA-2 trial.</p> <p>Verma S, O'Shaughnessy J, Burris H.A et al. Health-related quality of life of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer treated with ribociclib + letrozole: results from MONALEESA-2.</p> <p>Abstracts:                      (Andre et al., 2017); (André et al., 2016); (Blackwell et al., 2018); (Campone et al., 2017); (Grischke et al., 2016); (Hortobagyi et al., 2018a); (Hortobagyi et al., 2016a); (Hortobagyi et al., 2017); (O'Shaughnessy et al., 2017); (Janni et al., 2016); (Janni et al., 2017a); (Janni et al., 2017b); (Janni et al., 2017c); (Sonke et al., 2017); (Spazzapan et al., 2017); (Tolaney et al., 2018); (Verma et al., 2017a); (Verma et al., 2017b); (Verma et al., 2017c); (Yap et al., 2016); (Yardley et al., 2018).</p>	<p>Breast Cancer Res Treat 2018; 169:469-79</p> <p>Breast Cancer Res Treat 2018;168:127-34</p> <p>Breast Cancer Res Treat 2018; 167:659-69</p> <p>Breast Cancer Res Treat 2018; 170:535-45</p>

Source: Table 2.2.1, pp54 of the submission.

6.6 The key features of the randomised trials used in the indirect comparison are summarised in Table 6.

**Table 6: Key features of the included evidence – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Abemaciclib vs. anastrozole or letrozole</b>						
MONARCH-3	493	R, DB, MC, ongoing.  Median duration of follow up: 26.7 months	Low, however, the ESC considered the risk of unblinding to be high due to the high rate of diarrhoea with abemaciclib	HR+/HER2- ABC	Primary: PFS Secondary: OS, ORR, Duration of response, DCR, CBR, safety and tolerability, EORTC QLQ- C30, EORTC QLQ-BR23, and EQ-5D-5L.  Exploratory outcomes: Pharmacokinetic profile	RDI
<b>Ribociclib vs. letrozole</b>						
MONALEESA-2	668	R, DB, MC, ongoing.  Median duration of follow up: 26.4 months	Low	HR+/HER2- ABC	Primary: PFS Secondary: OS, ORR, CBR, ECOG performance status (time to deterioration), Safety and tolerability, and EORTC QLQ- C30.  Exploratory outcomes: Time to response, duration of response Pharmacokinetic profile	RDI

ABC: Advanced breast cancer; CBR: complete response rate; DB: double blind; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast; EORTC QLQ-C30: Core 30; EuroQol 5-Dimension 5-Level; MC: multi-centre; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R: randomised; RDI: relative dose intensity.  
Source: Table 2.4.4, p66 and 2.4.5, p67 of the submission.

### **Comparative effectiveness**

6.7 Table 7 presents the results of the PFS and OS analyses from the MONARCH-3 trial.

Table 7: Results of PFS and OS across MONARCH-3

Trial ID	Abemaciclib + NSAI N = 328		Placebo + NSAI N =165		Difference in median	P value (log rank test)	Hazard ratio (95% CI)
	Number of events, n (%)	Median (95% CI) months	Number of events, n (%)	Median (95% CI) months			
MONARCH-3							
PFS (investigator assessed; ITT population)	138 (42.1)	28.2 (23.5, NR)	108 (65.5)	14.8 (11.2, 19.2)	13.4	p=0.000002 <sup>a</sup>	0.54 (0.42, 0.70) <sup>a</sup>
PFS (Independent Review; ITT population)	91 (27.7)	NR (NR, NR)	73 (44.2)	19.36 (16.37, 27.91)	-	p≤0.000001	0.47 (0.34, 0.64)
OS (ITT population, 3 Nov 2017 data cut)	63 (19.2)	NR (NR, NR)	30 (18.2)	NR (NR, NR)	-	p=0.8017 <sup>b</sup>	1.06 (0.68, 1.63) <sup>b</sup>

CI: confidence interval; ITT: Intention-to-treat; n: number of participants reporting data; N: total participants in group; NR= not reached; NSAI: nonsteroidal aromatase inhibitor; PFS: progression free survival; OS: overall survival.

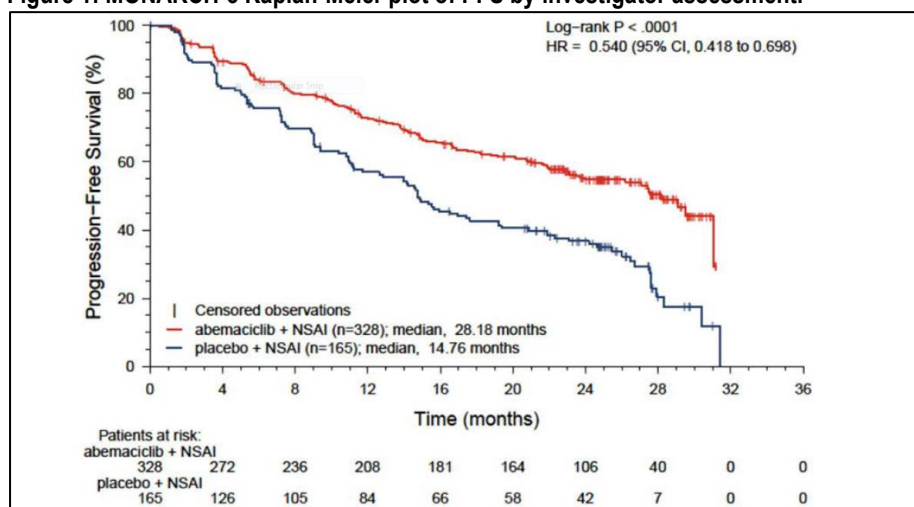
<sup>a</sup> Stratified by interactive web response system (IWRS) Endocrine Therapy and IWRS Nature of Disease

<sup>b</sup> Stratified by sensitivity to endocrine therapy and nature of disease per IWRS.

Source: Table JPBM.5.4, p19 and Table JPBM.5.7, p 29 of the MONARCH-3 CSR addendum body.

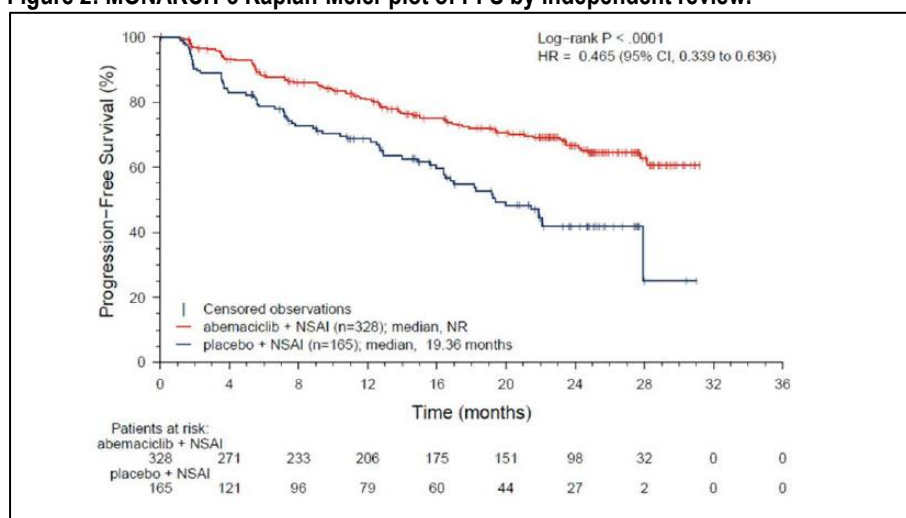
6.8 Figures 1 and 2 present PFS by investigator assessment and by independent review, respectively.

Figure 1: MONARCH-3 Kaplan-Meier plot of PFS by investigator assessment.



Source: Figure 2.5.1, p72 of the submission.

Figure 2: MONARCH-3 Kaplan-Meier plot of PFS by independent review.



Source: Figure 2.5.2, p72 of the submission.

- 6.9 Treatment with abemaciclib was associated with an increase in investigator-assessed PFS compared with placebo (abemaciclib plus NSAID arm: median 28.2 months [95% CI: 23.5, not reached]; placebo plus NSAID: median 14.8 months [95% CI: 11.2, 19.2]). The HR was statistically significant: 0.54 (95% CI: 0.42, 0.70; P<0.001).
- 6.10 OS data are still immature. Maturity of OS data is expected mid-2021 for MONARCH-3 (p56 of the submission). The HR for OS on the first 93 deaths was 1.06 (95% CI: 0.68, 1.63), favouring placebo, however the difference was not statistically significant (P= 0.8017). Fifteen deaths (4.6%) occurred during or within 30 days of treatment in the abemaciclib arm (vs 3 (1.9%) in the placebo arm), which were predominantly respiratory and (venous thromboembolic events) VTE deaths. The PSCR provided ad hoc, updated interim OS results with 9 months further follow-up data on deaths in MONARCH-3 (Figure 3). There was a total of 131 deaths, [REDACTED] % in abemaciclib and [REDACTED] % in placebo arm, with a HR for OS of [REDACTED] (95% CI: [REDACTED]). The long-term benefit of abemaciclib is uncertain. Ribociclib also had immature OS data at the time of its PBAC assessment, but with a HR of 0.75 (95% CI: 0.52, 1.09) (p= 0.059).

Figure 3: Updated interim MONARCH-3 Kaplan-Meier plot of OS (data cut: 31 July 2018).



Source: Figure 1, PSCR. Note: HRs stratified by endocrine therapy and nature of disease; p-Value (2-sided) by log-rank stratified for comparing with placebo + NSAI.

6.11 Quality of life (QoL) was similar across the treatment arms of MONARCH-3. Two domains differed by more than 5 points (the nominated minimum clinically meaningful difference) and patients in the abemaciclib plus NSAI arm reported lower scores on: the symptom domain of diarrhoea (LS mean difference [SE] of 18.68 [1.80]) of the EORTC QLQ-C30; and the body image domain (LS mean difference [SE] of -5.11 [1.95]) of the EORTC QLQ-BR23 (p75 of the submission). The EQ-5D-5L index value and VAS scores were similar between treatment arms.

6.12 Table 8 presents the indirect comparison of PFS by investigator assessment and independent review conducted by the submission. The intention-to-treat (ITT) population was used for the comparison of PFS.

Table 8: Indirect comparisons of PFS by investigator assessment and independent review; ITT population

Trial	Comparison	Test n/N (%)	Control n/N (%)	Test Median, Months (95% CI)	Control Median, Months (95% CI)	Hazard Ratio (95% CI)
<b>PFS by investigator assessment, ITT population</b>						
MONARCH-3	ABE + NSAI vs. PBO + NSAI	138/328 (42.1)	108/165 (65.5)	28.2 (23.5, NR)	14.8 (11.2, 19.2)	0.54 (0.42, 0.70)
MONALEESA-2	RIB + NSAI vs. PBO + NSAI	140/334 (41.9)	205/334 (61.4)	25.3 (23.0, 30.3)	16.0 (13.4, 18.2)	0.57 (0.46, 0.70)
<b>Indirect comparison abemaciclib + NSAI vs. ribociclib + NSAI</b>						0.95 (0.68, 1.33) P=0.768
<b>PFS by independent review, ITT population</b>						
MONARCH-3	ABE + NSAI vs. PBO + NSAI	91/328 (27.7)	73/165 (44.2)	NR (NR, NR)	19.4 (16.4, 27.9)	0.46 (0.34, 0.64)
MONALEESA-2	RIB + NSAI vs. PBO + NSAI	70/334 (21.0)	100/334 (29.9)	NR (30.3, NR)	NR (24.1, NR)	0.56 (0.41, 0.77)
<b>Indirect comparison abemaciclib + NSAI vs. ribociclib + NSAI</b>						0.82 (0.53, 1.28) P=0.390

ABE: abemaciclib; ITT: intention-to-treat; NSAI: non-steroidal aromatase inhibitor; PFS: progression-free survival; PBO: placebo; RIB: ribociclib

Source: Table 2.6.2 and Table 2.6.4 pp89-90 of the submission.

- 6.13 The submission did not specify a non-inferiority margin, however the March 2018 PBAC submission for palbociclib for a similar indication specified a non-inferiority margin of 1.4 (based on a published value for early breast cancer (Tanaka et al 2012) as no studies specific to advanced breast cancer were identified (palbociclib Public Summary Document (PSD), March 2018, paragraph 5.11).<sup>1</sup>
- 6.14 The indirect comparison of PFS by independent review resulted in a HR of 0.82 (95% CI 0.53, 1.28; P=0.390) (p90 of the submission). The indirect comparison of investigator-assessed PFS resulted in a HR of 0.95 (95% CI 0.68, 1.33; P=0.768) (p88 of the submission). The upper 95% confidence interval of the indirect comparison presented in the abemaciclib submission meets the non-inferiority margin of 1.4, which was nominated in the March 2018 PBAC submission for palbociclib.
- 6.15 However, more patients experienced progression with placebo plus NSAI (common reference arm) in the MONARCH-3 trial compared to the MONALEESA-2 trial. This may be because the MONARCH-3 trial had more patients with de novo metastatic breast cancer (39.8% versus 34.0%) and more patients with  $\geq 3$  sites of metastases (46.5% versus 34.0%). This suggests there are some issues with exchangeability between the trials.
- 6.16 The PSCR acknowledged that independently reviewed PFS event rates for both MONARCH-3 and MONALEESA-2 trials were lower than investigator-assessed PFS event rates and that the reason for this difference was uncertain. The PSCR speculated that this may be due to the trials defining bone metastases differently.
- 6.17 The primary outcome of the study was investigator-reported PFS. The PSCR argued that PFS is a clinically relevant outcome as it is linked to QoL. The ESC noted that while the trial demonstrated a benefit in terms of PFS compared to placebo, there was no difference observed in QoL. The ESC considered there was potential for investigator bias as almost all of the treatment group could have been identified by the side effect of diarrhoea.
- 6.18 The submission did not present an indirect comparison of overall survival.
- 6.19 The submission stated that MONARCH-3 had a higher proportion of Asian patients (30%) than would be expected in the Australian setting (approximately 5%). The MONARCH study reported that the Asian population had a greater PFS survival hazard ratio than the Caucasian population (HR 0.30 [95% CI 0.17 to 0.52] versus HR 0.69 [95% CI 0.48 to 0.99]). The ESC questioned if the results of the trial could be translated to the Australian population given the PBS population is likely to have a lower prevalence of Asian patients than the trial population. The pre-PBAC noted the treatment effect of abemaciclib plus NSAI and ribociclib plus NSAI were similar in the Asian subpopulation (HR 0.34 [95% CI: 0.21, 0.54] and HR 0.37 [95% CI: 0.18, 0.76]

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<sup>1</sup> 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.

respectively) and Caucasian subpopulation (HR 0.66 [95% CI: 0.48, 0.92] and HR 0.61 [95% CI: 0.49, 0.78], respectively). The pre-PBAC response argued that it may be assumed that the effectiveness of abemaciclib in the Australian clinical practice setting will be similar to that of ribociclib.

### Comparative harms

6.20 Table 9 presents safety results from the MONARCH-3 trial.

6.21 Almost all patients in the trial experienced an adverse event (AE) (98.8% versus 94.4% in the abemaciclib plus NSAID and placebo plus NSAID, respectively) (p78 of the submission).

**Table 9: Summary of key adverse events in the trials**

MONARCH-3 <sup>b</sup>	Abemaciclib + NSAID N = 327	Placebo + NSAID N = 161	RR (95% CI)
Patients with ≥1 TEAE	323 (98.8)	152 (94.4)	<b>1.046 (1.006, 1.088)</b>
Patients with ≥1 SAE	102 (31.2)	27 (16.8)	<b>1.860 (1.272, 2.720)</b>
Patients who discontinued study treatment due to an AE	54 (16.5)	5 (3.1)	5.317 (2.169, 13.034)
Patients who discontinued study treatment due to an SAE	21 (6.4)	5 (3.1)	2.068 (0.794, 5.384)
Patients who died due to an AE on study treatment <sup>c</sup>	8 (2.4)	2 (1.2)	1.969 (0.423, 9.168)
Patients who died due to AE ≤30d of disc. study treatment	3 (0.9)	0	3.446 (0.179, 66.326) <sup>a</sup>
Patients with diarrhoea, Grade ≥3	31 (9.5)	2 (1.2)	<b>7.631 (1.849, 31.491)</b>

AE: adverse event; CI: confidence interval; n: number of participants reporting data; N: total participants in group; NSAID: nonsteroidal aromatase inhibitor; RD: risk difference; RR: relative risk; SAE: serious adverse event(s); TEAE: treatment-emergent adverse event.

Note: Bold text indicates a statistically significant value.

<sup>a</sup> 0.5 added to the intervention and comparator arms.

<sup>b</sup> Patients may be counted in >1 category.

<sup>c</sup> Deaths are also included as SAEs and discontinuations due to AEs.

Source: Table 2.5.5, p 78 of the submission and compiled during the evaluation.

6.22 The most frequently observed AE of any grade was diarrhoea (82.3% versus 32.3% in the abemaciclib plus NSAID and placebo plus NSAID, respectively) (p59 of the submission). The majority of cases were grade 1 or 2 (42.5% and 30.3%, respectively), with 9.5% being grade 3 (p78 of the submission). The ESC considered there was potential for investigator bias as almost all of the treatment group could have been identified by the side effect of diarrhoea. The pre-PBAC response noted that the vast majority of diarrhoea events reported in MONARCH 3, for both the abemaciclib plus NSAID arm and the placebo plus NSAID arm, were of low grade (grade 1 or 2) severity. The pre-PBAC response considered it was therefore unlikely that the frequency or severity of diarrhoea adverse events in MONARCH 3 led to inadvertent unblinding of investigators. The PBAC considered that both MONARCH-3 and MONALESSA-2 carried risk of inadvertent unblinding due to AE occurrence which were mitigated in efficacy assessment by a blinded committee.

- 6.23 Anti-diarrhoeal medication was taken by 74.3% of patients experiencing diarrhoea (61.2% of the safety population) (p79 of the submission).
- 6.24 A higher proportion of patients in the intervention arm suffered from neutropenia compared with the control arm (all grades: 43.7% versus 1.9%) (Table 2.5.6, p80 of the submission).
- 6.25 Table 10 presents the indirect comparison of the safety results conducted by the submission.

Table 10: Indirect comparisons of adverse events; Safety population

Trial	Comparison	Test n/N (%)	Control n/N (%)	Risk Difference (95% CI)	Odds Ratio (95% CI)	Risk Ratio (95% CI)
<b>Patients reporting ≥1 Grade 3/4 AE</b>						
MONARCH-3	ABE + NSAID vs. PBO + NSAID	191/327 (58.4)	40/161 (24.8)	0.34 (0.25, 0.42)	4.25 (2.79, 6.46)	2.35 (1.77, 3.12)
MONALEESA-2	RIB + NSAID vs. PBO + NSAID	288/334 (86.2)	123/330 (37.3)	0.49 (0.43, 0.55)	10.54 (7.18, 15.45)	2.31 (2, 2.68)
Indirect Comparison	ABE + NSAID vs. RIB + NSAID			<b>-0.15 (-0.26, -0.05) P=0.005</b>	<b>0.4 (0.23, 0.71) P=0.002</b>	1.02 (0.74, 1.4) P=0.921
<b>Patients reporting ≥1 Grade 3 or 4 diarrhoea</b>						
MONARCH-3	ABE + NSAID vs. PBO + NSAID	31/327 (9.5)	2/161 (1.2)	0.08 (0.05, 0.12)	8.33 (1.97, 35.24)	7.63 (1.85, 31.49)
MONALEESA-2	RIB + NSAID vs. PBO + NSAID	8/334 (2.4)	3/330 (0.9)	0.01 (0, 0.03)	2.67 (0.7, 10.17)	2.63 (0.71, 9.84)
Indirect Comparison	ABE + NSAID vs. RIB + NSAID			<b>0.07 (0.03, 0.11) P=0.001</b>	3.11 (0.44, 22.24) P=0.258	2.9 (0.42, 20.07) P=0.282
<b>Patients reporting ≥1 Grade 3 or 4 neutropenia</b>						
MONARCH-3	ABE + NSAID vs. PBO + NSAID	78/327 (23.9)	2/161 (1.2)	0.23 (0.18, 0.28)	24.9 (6.03, 102.78)	19.2 (4.78, 77.16)
MONALEESA-2	RIB + NSAID vs. PBO + NSAID	207/334 (62.0)	4/330 (1.2)	0.61 (0.55, 0.66)	132.84 (48.36, 364.88)	51.13 (19.24, 135.91)
Indirect Comparison	ABE + NSAID vs. RIB + NSAID			<b>-0.38 (-0.45, -0.31) P&lt;0.001</b>	0.19 (0.03, 1.07) P=0.059	0.38 (0.07, 2.06) P=0.259
<b>Patients reporting ≥1 Grade 3 or 4 leucopenia</b>						
MONARCH-3	ABE + NSAID vs. PBO + NSAID	28/327 (8.6)	1/161 (0.6)	0.08 (0.05, 0.11)	14.98 (2.02, 111.14)	13.79 (1.89, 100.42)
MONALEESA-2	RIB + NSAID vs. PBO + NSAID	71/334 (21.3)	3/330 (0.9)	0.2 (0.16, 0.25)	29.43 (9.16, 94.49)	23.38 (7.44, 73.49)
Indirect Comparison	ABE + NSAID vs. RIB + NSAID			<b>-0.12 (-0.18, -0.07) P&lt;0.001</b>	0.51 (0.05, 5.17) P=0.568	0.59 (0.06, 5.84) P=0.651

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Trial	Comparison	Test n/N (%)	Control n/N (%)	Risk Difference (95% CI)	Odds Ratio (95% CI)	Risk Ratio (95% CI)
<b>Patients reporting ≥1 Grade 3 or 4 anaemia</b>						
MONARCH-3	ABE + NSAI vs. PBO + NSAI	23/327 (7)	2/161 (1.2)	0.06 (0.03, 0.09)	6.01 (1.4, 25.84)	5.66 (1.35, 23.72)
MONALEESA-2	RIB + NSAI vs. PBO + NSAI	8/334 (2.4)	4/330 (1.2)	0.01 (-0.01, 0.03)	2 (0.6, 6.71)	1.98 (0.6, 6.5)
Indirect Comparison	ABE + NSAI vs. RIB + NSAI			<b>0.05 (0.01, 0.08)</b> P=0.018	3.01 (0.45, 19.99) P=0.255	2.87 (0.44, 18.46) P=0.268
<b>Patients reporting ≥1 Grade 3 or 4 abnormal LFTs</b>						
MONARCH-3	ABE + NSAI vs. PBO + NSAI	30/327 (9.2)	3/161 (1.9)	0.07 (0.04, 0.11)	5.32 (1.6, 17.71)	4.92 (1.53, 15.89)
MONALEESA-2	RIB + NSAI vs. PBO + NSAI	34/334 (10.2)	8/330 (2.4)	0.08 (0.04, 0.11)	4.56 (2.08, 10.01)	4.2 (1.97, 8.93)
Indirect Comparison	ABE + NSAI vs. RIB + NSAI			0 (-0.06, 0.05) P=0.868	1.17 (0.28, 4.91) P=0.834	1.17 (0.29, 4.73) P=0.823
<b>Patients reporting ≥1 serious adverse event</b>						
MONARCH-3	ABE + NSAI vs. PBO + NSAI	102/327 (31.2)	27/161 (16.8)	0.14 (0.07, 0.22)	2.25 (1.4, 3.62)	1.86 (1.27, 2.72)
MONALEESA-2	RIB + NSAI vs. PBO + NSAI	85/334 (25.4)	51/330 (15.5)	0.1 (0.04, 0.16)	1.87 (1.27, 2.75)	1.65 (1.21, 2.25)
Indirect Comparison	ABE + NSAI vs. RIB + NSAI			0.04 (-0.05, 0.14) P=0.375	1.2 (0.65, 2.22) P=0.551	1.13 (0.69, 1.85) P=0.627
<b>Patients with ≥1 dose reduction</b>						
MONARCH-3	ABE + NSAI vs. PBO + NSAI	152/327 (46.5)	10/161 (6.2)	0.4 (0.34, 0.47)	13.12 (6.67, 25.78)	7.48 (4.06, 13.79)
MONALEESA-2	RIB + NSAI vs. PBO + NSAI	182/334 (54.5)	14/330 (4.2)	0.5 (0.44, 0.56)	27.03 (15.18, 48.13)	12.84 (7.62, 21.65)
Indirect Comparison	ABE + NSAI vs. RIB + NSAI			<b>-0.1 (-0.19, -0.01)</b> P=0.025	0.49 (0.2, 1.18) P=0.111	0.58 (0.26, 1.3) P=0.188

ABE: abemaciclib; LFTs: liver function tests; NSAI: non-steroidal aromatase inhibitor; PBO: placebo; RIB: ribociclib  
Sources: Table 2.6.5, p92 of the submission. Note: Bold text indicates a statistically significant value.

- 6.26 Compared with ribociclib plus NSAI, fewer patients treated with abemaciclib plus NSAI reported at least one Grade 3 or 4 AE and experienced Grade  $\geq 3$  neutropenia; and more patients treated with abemaciclib plus NSAI experienced Grade  $\geq 3$  diarrhoea and anaemia. The ESC noted that the neutropenia with CDK inhibitors is rapidly reversible and rarely leads to febrile neutropenia (1.5% in MONALEESA-2).
- 6.27 The FDA PI noted that 5% of patients treated with abemaciclib plus NSAI experienced VTEs, compared to 0.6% of patients in the control arm (Section 5.4, p5 of the FDA PI). Two deaths due to VTEs were reported in the Development Safety Update Report (DSUR) (Appendix 1 of the abemaciclib DSUR).

### ***Clinical claim***

- 6.28 The submission described abemaciclib plus NSAI as “clinically equivalent” in terms of effectiveness and safety compared to ribociclib plus NSAI (p98 of the submission).
- 6.29 The ESC considered the clinical claim in terms of PFS to be reasonable as the upper 95% confidence interval of the indirect comparison met the non-inferiority criterion specified in the March 2018 PBAC submission for palbociclib. The ESC noted that, given the immaturity of the survival data for abemaciclib, the submission did not present an indirect comparison of OS.
- 6.30 In its consideration of a previous submission for ribociclib (which claimed superior comparative effectiveness for ribociclib plus NSAI over letrozole alone based on the outcome of PFS), the PBAC expressed a concern that the immaturity of the OS data resulted in a high degree of uncertainty in the assessment of the magnitude of long-term benefit (ribociclib PSD, March 2018, paragraph 5.13). This concern is also likely to apply to abemaciclib.
- 6.31 The therapeutic conclusion regarding safety in the submission was based on an indirect comparison of patients reporting Grade 3/4 AEs. The safety profiles of abemaciclib and ribociclib are different, so the submission’s claim of clinical equivalence is uncertain. In particular, abemaciclib was associated with a numerically higher incidence of diarrhoea (mainly grade 1 and 2). A higher incidence of VTEs was reported with abemaciclib plus NSAI versus NSAI alone. The ESC considered there was potential for investigator bias as almost all of the treatment group could have been identified by the side effect of diarrhoea.
- 6.32 The PBAC considered that the claim of non-inferior comparative effectiveness to ribociclib plus NSAI was reasonable in terms of PFS. The PBAC noted that the OS data was immature, and considered that there was a high degree of uncertainty in the magnitude of long-term benefit with abemaciclib plus NSAI compared with placebo.
- 6.33 The PBAC considered that the claim of non-inferior safety was uncertain as abemaciclib has a different safety profile to ribociclib.

### ***Economic analysis***

- 6.34 The submission presented a cost-minimisation analysis on the basis that abemaciclib and ribociclib are clinically equivalent in terms of effectiveness and safety.

6.35 Table 11 presents the results of the cost-minimisation analysis of abemaciclib and ribociclib.

**Table 11: Results of the cost-minimisation analysis of abemaciclib and ribociclib**

	Component	Calculation	Abemaciclib	Ribociclib
A	Treatment cycle		28 days of a 28-day cycle	21 days of a 28-day cycle
B	Mean dose (mg/day)#		300 mg x 79.21% RDI = 237.63	600 mg x 79.5% RDI = 476.8
C	Mg per 28-day treatment cycle	A*B	6,653.64	10,012.80
D	Dose duration		79.1 weeks (19.78 cycles)	87.9 weeks (21.98 cycles)
E	Total mg per treatment course	C*D	131,609.00	220,081.34
F	Cost per mg (PEMP)	G/E		
G	Total costs of CDK4/6 treatment per patient	I-H		
H	Associated treatment costs <sup>^</sup>			
I	Total treatment cost per patient <sup>^</sup>	G+H		

Source: Table 3.4.3, p106 of the submission, Attachment A5.1\_Abemaciclib Section 3 Model. Calculations have been updated using PSCR. Abbreviations: PEMP = proportional ex-manufacturer price, RDI = relative dose intensity.

#Values taken from submission. Mean dose (mg/day) accounts for the RDI. Source: abemaciclib RDI – MONARCH-3 CSR Addendum, p40; ribociclib RDI and dose duration - Hortobagyi et al., 2018 (p1543 (RDI) and p1545 (dose duration)). Dose duration originally reported in months (20.2 months ribociclib and 14.1 months placebo). Submission converted time to weeks (x4.35) for ease of comparison to MONARCH-3

<sup>^</sup>Costs updated in PSCR (p3). Cost offsets estimated to result from the PBS listing of abemaciclib, which would result in decreases in resource utilisation associated with ECG monitoring of the QT interval (required with ribociclib but not abemaciclib), and a small decrease in the usage of concomitant NSAIDs due to different durations of therapy. Cost of treating diarrhoea with loperamide is excluded (page 17 of submission). Cost offsets were updated in PSCR (p3): cost offset for ECG monitoring associated with ribociclib were corrected, 100% MBS fee applied. Cost of treating diarrhoea with loperamide was excluded.

6.36 The equi-effective doses were estimated in the submission as abemaciclib 237.63 mg/day [relative dose intensity (RDI) 79.21%], for 28 days of a 28-day cycle, over 79.1 weeks (total of 131,609.00 mg) and ribociclib 476.8 mg/day [RDI 79.5%], for 21 days of a 28-day cycle over 87.9 weeks (total of 220,081.34 mg).

6.37 The RDIs were estimated based on the mean dose of treatment received in the clinical trials (MONARCH-3 and MONALEESA-2). The evaluation considered this was reasonable.

6.38 The duration of treatment with abemaciclib (79.1 weeks) was shorter than ribociclib (87.9 weeks). The ESC considered that including a shorter duration of treatment with abemaciclib was inconsistent with the claim that abemaciclib and ribociclib are clinically equivalent in terms of PFS and noted that this resulted in a higher price for abemaciclib compared with assuming the same treatment duration. The PSCR argued that the in-trial treatment durations were recommended for cabozantinib (item 5.02, cabozantinib PSD, December 2017). The ESC noted that the differences in placebo treatment time in the current submission was greater than the cabozantinib consideration, where cabozantinib versus nivolumab with the common comparator of everolimus had similar median treatment times in the trials presented. Furthermore, the ESC noted that the duration of treatment was not taken into account in estimating the equi-effective doses for palbociclib and ribociclib (March 2018 ribociclib PSD).

6.39 The pre-PBAC response noted if treatment duration is not included in the calculations, the equi-effective doses of abemaciclib and ribociclib may be considered as:

abemaciclib 300 mg x 79.2% RDI x 28 days is equivalent to ribociclib 600 mg x 79.5% RDI x 21 days.

- 6.40 The full MBS fee (100%) was not applied for all patients, as per the Manual of resource items and their associated unit costs - December 2016 (Section 5) for the ECG MBS item number 11700 and additional routine laboratory monitoring (liver function tests under MBS item number 66512 during Cycle 5 and 6, additional blood counts during Cycle 5 and 6 under MBS item number 65070, and serum electrolytes for 6 weeks); therefore MBS costs were underestimated. The cost of loperamide for treating diarrhoea in patients on abemaciclib was excluded from the analysis. The PSCR corrected the cost offset for ECG monitoring associated with ribociclib to the base case. However, the PSCR stated there was uncertainty around the number of tests required, so these costs were presented in a sensitivity analysis. The PSCR stated that there was uncertainty regarding utilisation of loperamide, so these costs were presented in a sensitivity analysis.
- 6.41 The ESC considered it was not reasonable to exclude the loperamide costs given the high rates of diarrhoea associated with abemaciclib use. Additionally, the monitoring costs should have been included to accurately represent the cost of abemaciclib. However, the ESC noted the updated sensitivity analyses presented in the PSCR showed the costs of loperamide for diarrhoea and additional routine laboratory monitoring had minimal impact on the overall cost of abemaciclib.
- 6.42 Ribociclib is currently listed on the PBS under a Special Pricing Arrangement (SPA). The submission could not take into account the SPA for ribociclib as the effective price of ribociclib was unknown. Therefore, the submission utilised the published Proportional Ex-Manufacturer Price<sup>2</sup> (PEMP) of \$5,360.01 (for 600 mg/day dose) as the price for ribociclib for the cost minimisation analysis.

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

- 6.43 The submission estimated the drug cost/patient/course to be \$ [REDACTED] (see Table 11). The PSCR updated the cost to \$ [REDACTED] to include the estimated costs for ECG monitoring.

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

- 6.44 This submission was not considered by DUSC.
- 6.45 The submission applied an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of abemaciclib. The submission took a two-step approach. The first-step was to construct an estimate of the CDK 4 and 6 inhibitor market (i.e. number of patients) using epidemiology data and the second-

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<sup>2</sup> PBS prices for other pack sizes are calculated proportionally from the Approved Ex-Manufacturer Price (AEMP) for the pricing quantity. These prices are called proportional ex-manufacturer prices (PEMPs). Therefore, the price of ribociclib was based on the published PEMP, which is the AEMP of \$1786.67 for 200mg/day dose, multiplied by three for the 600mg/day dose.

step used a market share approach to predict the use of ribociclib and abemaciclib (i.e. financial impact). This was due to the immature nature of the number of scripts of ribociclib. The evaluation considered this was reasonable.

6.46 Table 12 presents the estimated use and financial implications.

**Table 12: Estimated use and financial implications**

	Year 1 2019	Year 2 2020	Year 3 2021	Year 4 2022	Year 5 2023	Year 6 2024
<b>Estimated extent of use</b>						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed <sup>a</sup>	█	█	█	█	█	█
<b>Estimated financial implications of abemaciclib</b>						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Estimated financial implications for ribociclib<sup>b</sup></b>						
Saving to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Copayments <sup>c</sup>	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Saving to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Estimated financial implications for NSAI<sup>d</sup></b>						
Saving to PBS/RPBS	█	█	█	█	█	█
Copayments	-█	-█	-█	-█	-█	-█
Saving to PBS/RPBS less copayments	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS <sup>d</sup>	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to PBS/RPBS/MBS	-\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

ECG: electrocardiogram, NSAI: non-steroidal aromatase inhibitor, PBS: pharmaceutical benefits scheme, RPBS: repatriation pharmaceutical benefits scheme; MBS: Medicare benefits schedule.

<sup>a</sup> Assuming █ scripts per year (█\*79.1/87.9) as estimated by the submission.

<sup>b</sup> Based on published DPMQ

<sup>c</sup> Copayments were corrected during evaluation

<sup>d</sup> ECGs avoided

Source: Table 4.5.2, p121 of submission; Attachment A6.1\_Abemaciclib Section 4 Model

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

6.47 The overall financial impact to the Australian Government health budget was estimated to be less than \$10 million over 6 years. The additional cost is due to:

- the uncertainty of the estimated increased proportion of patients eligible for CDK 4/6 treatment and those electing treatment with abemaciclib over ribociclib.
- uncertainty regarding the submission’s assumption of similar adherence rates between abemaciclib and ribociclib given patients using abemaciclib had higher rates of diarrhoea and treatment cycles between abemaciclib (28 days) and ribociclib (21 days) were different.

- The method used by the submission to estimate the number of ECGs avoided was uncertain which would impact on the calculation of the cost offsets. The approach used did not estimate the number of ECGs avoided using the number of patients no longer using ribociclib.
- The estimated cost of abemaciclib will be different because it was based on the published price of ribociclib as the effective price of ribociclib was unknown. The submission used an estimated DPMQ of \$ [REDACTED] for abemaciclib calculated from the cost of abemaciclib per mg ([REDACTED]) which was based on the published PEMP for the 600mg/day dose of ribociclib (\$5,360.01).

### ***Quality Use of Medicines***

6.48 The submission did not raise any concerns regarding the quality use of abemaciclib. The submission included a summary of a risk management plan to ensure the appropriate use of abemaciclib, monitoring regimens and managing AEs. This includes training and support towards healthcare professionals and a Consumer Medicine Information (CMI) website accessible by patients.

6.49 The submission did not include any proposal for a post-marketing surveillance study.

### ***Financial Management – Special Pricing Arrangements and Risk Sharing Arrangements***

6.50 The submission noted that an SPA applies to the listing of ribociclib. The sponsor has stated that an SPA is requested for abemaciclib and the terms of which will be negotiated with the Department should it be recommended for PBS listing.

6.51 There is an existing Deed of Agreement for ribociclib for locally advanced or metastatic breast cancer.

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

## **7 PBAC Outcome**

7.1 The PBAC deferred making a recommendation to list abemaciclib for the treatment of non-premenopausal patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer. However, the PBAC was of a mind to recommend abemaciclib on a cost minimisation basis to ribociclib, pending provision of a positive TGA Delegate's overview. The PBAC considered that abemaciclib would provide patients with an alternative to ribociclib for HR+, HER2- advanced breast cancer. The PBAC considered that abemaciclib + NSAID was non-inferior in terms of comparative effectiveness and safety compared with ribociclib + NSAID while noting there were differences between the safety profiles of abemaciclib and ribociclib. The PBAC considered the cost-minimisation analysis was reasonable when the equi-effective doses are calculated without the duration of therapy being taken into account, in line with the claim of non-inferior comparative effectiveness in terms of PFS.

- 7.2 The PBAC acknowledged the consumer comments, including from the Breast Cancer Network Australia and Medical Oncology Group of Australia, which were supportive of listing abemaciclib as an alternative treatment option for patients with HR+/HER2-advanced breast cancer.
- 7.3 The PBAC accepted ribociclib as the main comparator, noting that ribociclib is the only other CDK 4 and 6 inhibitor listed on the PBS for the same indication as abemaciclib. The PBAC also recalled that it recommended listing palbociclib for a similar indication at its March 2018 meeting.
- 7.4 The PBAC noted the major submission was based on an indirect comparison of two randomised trials: MONARCH-3 comparing abemaciclib plus NSAI (anastrozole or letrozole) to placebo plus NSAI; and MONALEESA-2 comparing ribociclib plus letrozole to placebo plus letrozole in postmenopausal women with HR+, HER2- advanced breast cancer who had no prior systemic therapy in the advanced disease setting.
- 7.5 The PBAC noted that abemaciclib resulted in a statistically significant improvement in PFS when compared with placebo plus NSAI where there was a median increase in investigator assessed PFS of 13.4 months (HR 0.54 (0.42, 0.7)) in MONARCH-3. However, the PBAC noted that the gain in PFS in the trial was not reflected in an improvement in QoL.
- 7.6 The PBAC noted that the OS data for MONARCH-3 was still immature. At the time of PBAC consideration, the sponsor provided ad hoc, updated interim OS results, which showed 9 months further follow-up data on deaths in MONARCH-3 which resulted in a HR for OS of [REDACTED] (95% CI: [REDACTED]). The updated difference in OS, although in favour of abemaciclib, was not statistically significant ( $p=[REDACTED]$ ). The PBAC recalled its consideration of ribociclib at its March 2018 meeting that the ribociclib submission also presented immature OS data from the MONALEESA-2 trial, with a HR of 0.746 (0.517, 1.078) ( $p=0.059$ ). Due to the immaturity of the OS data from MONARCH-3, the PBAC considered that there was a high degree of uncertainty in the magnitude of long-term benefit with abemaciclib plus NSAI compared with placebo.
- 7.7 The PBAC noted that the indirect comparison of abemaciclib plus NSAI compared with ribociclib plus NSAI resulted in an HR of 0.82 (95% CI 0.53, 1.28;  $P=0.390$ ) for PFS by independent review and an HR of 0.95 (95% CI 0.68, 1.33;  $P=0.768$ ) for investigator assessed PFS. The PBAC noted the upper 95% confidence interval of the indirect comparison presented in the abemaciclib submission met the non-inferiority criterion (1.4) specified in the March 2018 PBAC submission for palbociclib. Accordingly, the PBAC considered that abemaciclib plus NSAI may be considered non-inferior in terms of clinical effectiveness compared with ribociclib plus NSAI with regards to PFS.
- 7.8 The PBAC noted the high rate of adverse events associated with abemaciclib, with the majority of patients in the MONARCH-3 trial experiencing an AE (98.8%), of which 58.4% were Grade >3 (compared with 86.2% for those treated with ribociclib). The PBAC noted that 46.5% of patients had a dose reduction when using abemaciclib. The PBAC noted that diarrhoea was the most frequently observed AE when treated with abemaciclib (82.3%), with 72.8% of cases Grade 1 or 2, while 9.5% were Grade 3. The

PBAC also noted that when compared with ribociclib plus NSAID, fewer patients treated with abemaciclib plus NSAID reported Grade  $\geq 3$  neutropenia, although neutropenia with CDK inhibitors rarely leads to febrile neutropenia and is rapidly reversible. The PBAC also noted that use of abemaciclib is not associated with QT interval prolongation (heart rhythm disorder), which provides a CDK inhibitor treatment for patients with cardiac issues. The PBAC considered that the claim of non-inferior safety was uncertain, as abemaciclib has a different safety profile to ribociclib.

- 7.9 The PBAC noted that there are potential differences in costs between abemaciclib and ribociclib which cannot be estimated accurately. The PBAC noted the PSCR demonstrated the impact of these costs on the price was small and therefore, the PBAC considered that the additional costs were not required to be included in the cost-minimisation analysis.
- 7.10 The PBAC considered that the equi-effective doses for abemaciclib and ribociclib should be calculated without the duration of treatment from the trials being taken into account (79.1 weeks with abemaciclib and 87.9 weeks with ribociclib). The PBAC noted that including a shorter duration of treatment with abemaciclib was inconsistent with the claim that abemaciclib and ribociclib are clinically equivalent in terms of PFS. The PBAC also recalled previous considerations for ribociclib and palbociclib and noted that similarly excluding treatment duration for abemaciclib would be consistent. The PBAC therefore accepted the method of calculating the equi-effective doses in the pre-PBAC response (paragraph 6.39): abemaciclib 300 mg x 79.2% RDI x 28 days and ribociclib 600 mg x 79.5% RDI x 21 days.
- 7.11 The PBAC noted that there is a Risk Sharing Arrangement (RSA) in place to manage the total cost of ribociclib on the PBS. The PBAC considered that abemaciclib should join the existing RSA Subsidisation Caps for ribociclib and be subject to identical rebates should total expenditure on the two medicines exceed these Caps, to ensure there is no new net financial cost to Government.
- 7.12 The PBAC noted that abemaciclib is associated with a higher incidence of diarrhoea compared with ribociclib. The PBAC considered that diarrhoea was a meaningful adverse event associated with the treatment with abemaciclib that will have an impact on a patient's QOL. The PBAC therefore considered that it may be appropriate for any price agreed for abemaciclib to be lower per patient compared to ribociclib.
- 7.13 The PBAC considered that the estimated financial impact of listing abemaciclib is uncertain due to the issues discussed in paragraph 6.47. The PBAC considered the financial risk would be mitigated by joining the existing Deed of Agreement currently in place for ribociclib to ensure there is no net financial cost to the government.
- 7.14 The PBAC noted that interim OS results from the MONARCH-3 trial are expected to be available in 2021 and advised that, if listed, the sponsor should provide these results to the PBAC.
- 7.15 The PBAC recommended that the listing for abemaciclib should be in line with that with ribociclib and should also:

- restrict patients from using ribociclib in combination with abemaciclib,
- exclude patients who have been previously treated with an aromatase inhibitor for this indication (as aromatase inhibitors are standard of care in adjuvant settings);
- exclude patients who have been previously treated with ribociclib unless the patient has developed an intolerance to ribociclib of a severity necessitating permanent treatment withdrawal;
- remove the requirement for QT monitoring as abemaciclib is not associated with QT interval prolongation;
- a clinical criterion should be added to the 50 mg and 100 mg strengths of abemaciclib which allow for dosage reduction using the specified tablet; and
- not include grandfathering restriction.

7.16 The PBAC considered that upon listing abemaciclib, the following flow-on changes will need to be made to the current ribociclib listing:

- restrict patients from using ribociclib in combination with abemaciclib;
- update the criterion in the initial restriction, “patient must not have previously been treated with an aromatase inhibitor” by adding “for this indication” at the end, as aromatase inhibitors are standard of care in adjuvant settings; and,
- adding a criterion that a patient must not have been previously treated with abemaciclib unless the patient developed an intolerance to abemaciclib necessitating permanent treatment withdrawal.

**Outcome:**

Deferred

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor’s Comment**

The sponsor had no comment.

## **Addendum to the March 2019 PBAC Minutes:**

### **10 Purpose of Application**

- 10.1 At its March 2019 meeting, the PBAC deferred making a recommendation regarding the listing of abemaciclib as the TGA Delegates Request for ACM Advice (Delegate's Overview) or indicative TGA outcome was not available at the time of consideration. The PBAC was of a mind to recommend abemaciclib pending provision of the TGA Delegate's overview or other such advice supportive of the TGA registration of abemaciclib.
- 10.2 The sponsor provided the positive TGA Delegate's Summary on 28 March 2019. The TGA approval was received on 8 April 2019.

### **11 Background**

- 11.1 At its March 2019 meeting, the PBAC accepted ribociclib as the main comparator to abemaciclib, which at the time was the only other CDK 4 and 6 inhibitor listed on the PBS for the same indication as abemaciclib.
- 11.2 Since the consideration of abemaciclib in March 2019, palbociclib, another CDK 4 and 6 inhibitor, was listed on the PBS on 1 May 2019 for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced inoperable or metastatic breast cancer.
- 11.3 Palbociclib was recommended for listing at the March 2018 PBAC meeting. The PBAC recalled that at this meeting, ribociclib was considered a near market comparator and recommended that if ribociclib and palbociclib were both listed on the PBS, the listings should not allow palbociclib and ribociclib 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. For the consideration of abemaciclib, the PBAC considered that similar restriction flow-ons should apply if abemaciclib was listed.

### **12 PBAC Outcome**

- 12.1 The PBAC recommended the Authority Required listing of abemaciclib for the treatment of non-premenopausal patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer on a cost minimisation basis to ribociclib and palbociclib. Noting the TGA has registered abemaciclib for this indication, the PBAC was satisfied the remaining outstanding issues relating to the application were satisfactorily resolved.
- 12.2 The PBAC considered that abemaciclib would provide patients with an alternative to ribociclib and palbociclib for HR+, HER2- advanced breast cancer.
- 12.3 The PBAC recalled it considered a number of factors relating to the requested listing

at its March 2019 meeting, including:

- The nominated comparator ribociclib was appropriate and at the time was the only other CDK 4 and 6 inhibitor listed on the PBS for the same indication as abemaciclib.
- The PBAC considered that abemaciclib provided a statistically significant improvement in PFS when compared with placebo plus NSAID, where there was a median increase in investigator assessed PFS of 13.4 months (HR 0.54 (0.42, 0.7)) in the MONARCH-3 trial. The PBAC noted that this was not reflected in an improvement in Quality of life (QoL). The PBAC also noted that the indirect comparison of abemaciclib plus NSAID compared with ribociclib plus NSAID resulted in an HR of 0.82 (95% CI 0.53, 1.28; P=0.390) for PFS by independent review and an HR of 0.95 (95% CI 0.68, 1.33; P=0.768) for investigator assessed PFS. The PBAC noted the upper 95% confidence interval of the indirect comparison presented in the abemaciclib submission met the non-inferiority criterion (1.4) specified in the March 2018 PBAC submission for palbociclib. Accordingly, the PBAC considered that abemaciclib plus NSAID may be considered non-inferior in terms of clinical effectiveness compared with ribociclib plus NSAID with regards to PFS.
- The PBAC noted that OS data was immature, and although this was in favour of abemaciclib, the difference was not statistically significant. The PBAC considered there was a high degree of uncertainty in the magnitude of long-term benefit with abemaciclib plus NSAID compared with placebo.
- The PBAC noted a high rate of adverse events associated with abemaciclib (98.8% experiencing an AE), with diarrhoea being the most frequently observed (82.3%) in the MONARCH-3 trial. The PBAC noted fewer patients reported neutropenia when compared with ribociclib plus NSAID, and the use of abemaciclib is not associated with QT prolongation. The PBAC considered that the claim of non-inferior safety was uncertain, as abemaciclib has a different safety profile to ribociclib.
- Therefore, the PBAC maintained that abemaciclib + NSAID was non-inferior in terms of comparative effectiveness and safety compared with ribociclib + NSAID while noting there were differences between the safety profiles of abemaciclib and ribociclib.

12.4 The PBAC maintained the view that the cost-minimisation analysis of abemaciclib and ribociclib was reasonable when the equi-effective doses are calculated without the duration of therapy being taken into account, in line with the claim of non-inferior comparative effectiveness in terms of PFS. The PBAC also noted that in March 2018 it recommended equi-effective doses for ribociclib and palbociclib. Therefore, the PBAC considered that abemaciclib should be cost-minimised to ribociclib and palbociclib.

12.5 The PBAC accepted the following equi-effective doses:

- abemaciclib 300 mg x 79.2% RDI x 28 days;

- ribociclib 600 mg x 79.5% RDI x 21 days; and
  - palbociclib █████ mg x mean RDI of █████ % x 21 days.
- 12.6 The PBAC noted that there is a Risk Sharing Arrangement (RSA) in place to manage the total cost of both ribociclib and palbociclib on the PBS. The PBAC considered that abemaciclib should join the existing RSA Subsidisation Caps for ribociclib and palbociclib, and be subject to identical rebates should total expenditure of the three medicines exceed these Caps, to ensure there is no new net financial cost to Government.
- 12.7 The PBAC noted that abemaciclib is associated with a higher incidence of diarrhoea compared with ribociclib. The PBAC considered that diarrhoea was a meaningful adverse event associated with the treatment with abemaciclib that will have an impact on a patient's QoL. Therefore, the PBAC was of the view that a listing for abemaciclib should result in a cost saving to Government.
- 12.8 The PBAC recalled that interim OS results from the MONARCH-3 trial are expected to be available in 2021 and advised that, if listed, the sponsor should provide these results to the PBAC.
- 12.9 The PBAC advised the Early Supply Rule should apply to the listings of abemaciclib as this aligns with the recommendation for ribociclib and palbociclib.
- 12.10 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that abemaciclib should be treated as interchangeable on an individual patient basis with both ribociclib and palbociclib.
- 12.11 The PBAC advised that abemaciclib is not suitable for prescribing by nurse practitioners.
- 12.12 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.
- 12.13 The PBAC recommended that the listing for abemaciclib should be in line with the listings for ribociclib and palbociclib. The abemaciclib listing should also:
- restrict patients from using ribociclib or palbociclib in combination with abemaciclib;
  - restrict patients who have previously been treated with an aromatase inhibitor for advanced or metastatic breast cancer from using abemaciclib;
  - exclude patients who have been previously treated with ribociclib or palbociclib unless the patient has developed an intolerance to ribociclib or palbociclib of a severity necessitating permanent treatment withdrawal;
  - no requirement for QT monitoring is required in the abemaciclib listing as abemaciclib is not associated with QT interval prolongation, which is the same as palbociclib;

- a clinical criterion should be added to the 50 mg and 100 mg strengths of abemaciclib which allow for dosage reduction using the specified tablet; and
- not include grandfathering restriction.

These have been accounted for in the recommended listing in Section 11.

12.14 The PBAC considered that upon listing abemaciclib, the following flow-on changes will need to be made to the current ribociclib and palbociclib listings:

- restrict patients from using ribociclib in combination with abemaciclib;
- restrict patients from using palbociclib in combination with abemaciclib; and,
- adding a criterion that a patient must not have been previously treated with abemaciclib unless the patient developed an intolerance to abemaciclib necessitating permanent treatment withdrawal.

These amendments are outlined in the flow-on changes to listing in Section 11.

**Outcome:**

Recommended

### 13 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Proprietary Name	Manufacturer
ABEMACICLIB 150 mg tablet, 56 100 mg tablet, 56 50 mg tablet, 56	1	56	5	VERZENIO™	Eli Lilly Australia Pty Ltd

<b>Category/ Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	N/A
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Breast cancer
<b>PBS Indication:</b>	Locally advanced or metastatic breast cancer
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	<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

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<b>Clinical criteria:</b>	<p>Patient must not have previously been treated with an aromatase inhibitor for advanced or metastatic breast cancer  AND  Patient must not have previously been treated with ribociclib or palbociclib  OR  Patient must have developed an intolerance to ribociclib or palbociclib of a severity necessitating permanent treatment withdrawal  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.  AND  The treatment must be in combination with anastrozole or letrozole  AND  The treatment must not be in combination with ribociclib or palbociclib  AND  <b>Patient must require dosage reduction requiring 100 mg tablet <sup>a</sup></b>  <b>Patient must require dosage reduction requiring 50 mg tablet <sup>b</sup></b></p>
<b>Population criteria:</b>	Patient must not be premenopausal
<b>Administrative Advice</b>	<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  Special Pricing Arrangement apply</p>

a Criterion only included in the restriction for 100 mg strength

b Criterion only included in the restriction for 50 mg strength

<b>Treatment phase:</b>	Continuing treatment
<b>Restriction:</b>	<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
<b>Treatment criteria:</b>	<p>The treatment must be in combination with anastrozole or letrozole  AND  The treatment must not be in combination with ribociclib</p>
<b>Clinical criteria:</b>	<p>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  AND  The treatment must be in combination with anastrozole or letrozole  AND  The treatment must not be in combination with ribociclib or palbociclib  AND  <b>Patient must require dosage reduction requiring 100 mg tablet <sup>a</sup></b>  <b>Patient must require dosage reduction requiring 50 mg tablet <sup>b</sup></b></p>
<b>Population criteria:</b>	Patient must not be premenopausal
<b>Prescriber Instructions</b>	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.

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<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised Special Pricing Arrangement apply
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a Criterion only included in the restriction for 100 mg strength

b Criterion only included in the restriction for 50 mg strength

Flow-on changes to listings are required for palbociclib (items 11698Q, 11699R and 11700T) and ribociclib (11385F, 11386G and 11397W). The listings for palbociclib and ribociclib should be amended as follows should abemaciclib be listed on the PBS. The changes are highlighted in italics and strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Proprietary Name	Manufacturer
PALBOCICLIB 75 mg capsule, 21 100 mg capsule, 21 125 mg capsule, 21	1	21	5	IBRANCE	Pfizer Australia Pty Ltd

<b>Category/ Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	N/A
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Breast cancer
<b>PBS Indication:</b>	Locally advanced or metastatic breast cancer
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	<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
<b>Clinical criteria:</b>	Patient must not have previously been treated with an aromatase inhibitor for advanced or metastatic breast cancer AND Patient must not have previously been treated with ribociclib <i>or abemaciclib</i> OR Patient must have developed an intolerance to ribociclib <i>or abemaciclib</i> of a severity necessitating permanent treatment withdrawal 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. AND The treatment must be in combination with anastrozole or letrozole AND The treatment must not be in combination with ribociclib <i>or abemaciclib</i>

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<b>Population criteria:</b>	Patient must not be premenopausal
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised Special Pricing Arrangement apply

<b>Treatment phase:</b>	Continuing treatment
<b>Restriction:</b>	<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
<b>Clinical criteria:</b>	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 according to the Response Evaluation Criteria In Solid Tumours (RECIST), AND The treatment must be in combination with anastrozole or letrozole AND The treatment must not be in combination with ribociclib <i>and abemaciclib</i>
<b>Population criteria:</b>	Patient must not be premenopausal
<b>Prescriber Instructions</b>	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.
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised Special Pricing Arrangement apply

<b>Treatment phase:</b>	Initial treatment – Grandfather patients
<b>Restriction:</b>	<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

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<b>Clinical criteria:</b>	<p>Patient must have received non-PBS subsidised treatment with this drug for this condition prior to 1 May 2019, AND Patient must not have previously been treated with an aromatase inhibitor prior to initiating treatment with this drug for this condition AND Patient must not have previously been treated with ribociclib <i>or</i> abemaciclib OR Patient must have developed an intolerance to ribociclib <i>or</i> abemaciclib of a severity necessitating permanent treatment withdrawal 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 prior to initiating treatment with this drug for this condition. AND Patient must not have developed disease progression while 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) AND The treatment must be in combination with anastrozole or letrozole AND The treatment must not be in combination with ribociclib <i>or</i> abemaciclib</p>
<b>Population criteria:</b>	Patient must not be premenopausal
<b>Prescribing Instructions</b>	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
<b>Administrative Advice</b>	<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 Special Pricing Arrangement apply</p>

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	№.of Rpts	Proprietary Name	Manufacturer
RIBOCICLIB		21			Novartis
200 mg film-coated tablet, 21	1	42	5	KISQALI	Pharmaceuticals Australia Pty Ltd
200 mg film-coated tablet, 42		63			
200 mg film-coated tablet, 63					

<b>Category/ Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	N/A
<b>Severity:</b>	Locally advanced or metastatic
<b>Condition:</b>	Breast cancer
<b>PBS Indication:</b>	Locally advanced or metastatic breast cancer
<b>Treatment phase:</b>	Initial treatment

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<b>Restriction:</b>	<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
<b>Clinical criteria:</b>	<p>Patient must not have previously been treated with an aromatase inhibitor for advanced or metastatic breast cancer            AND            Patient must not have previously been treated with palbociclib <i>or</i> <i>abemaciclib</i>            OR            Patient must have developed an intolerance to palbociclib <i>or</i> <i>abemaciclib</i> of a severity necessitating permanent treatment withdrawal            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.            AND            The treatment must be in combination with anastrozole or letrozole            AND            The treatment must not be in combination with palbociclib <i>or</i> <i>abemaciclib</i>            AND  <b>Patient must require dosage reduction requiring a pack of 21 tablets <sup>a</sup></b>  <b>Patient must require dosage reduction requiring a pack of 42 tablets <sup>b</sup></b></p>
<b>Population criteria:</b>	Patient must not be premenopausal.
<b>Caution</b>	QT monitoring is required for patients treated with this drug.
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

a Criterion only included in the restriction for 21 tablet pack

b Criterion only included in the restriction for 42 tablet pack

<b>Treatment phase:</b>	Continuing treatment
<b>Restriction:</b>	<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
<b>Clinical criteria:</b>	<p>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,            AND            The treatment must be in combination with anastrozole or letrozole            AND            The treatment must not be in combination with palbociclib <i>or</i> <i>abemaciclib</i>            AND  <b>Patient must require dosage reduction requiring a pack of 21 tablets <sup>a</sup></b>  <b>Patient must require dosage reduction requiring a pack of 42 tablets <sup>b</sup></b></p>

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<b>Population criteria:</b>	Patient must not be premenopausal.
<b>Prescribing Instructions</b>	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.
<b>Caution</b>	QT monitoring is required for patients treated with this drug.
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised Special Pricing Arrangement apply

a Criterion only included in the restriction for 21 tablet pack

b Criterion only included in the restriction for 42 tablet pack

<b>Treatment phase:</b>	Initial treatment – Grandfather patients
<b>Restriction:</b>	<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
<b>Clinical criteria:</b>	<p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to 1 July 2018 AND            Patient must not have previously been treated with an aromatase inhibitor for this condition prior to initiating treatment with this drug for this condition AND            Patient must not have previously been treated with palbociclib <i>or</i> <i>abemaciclib</i> OR            Patient must have developed an intolerance to palbociclib <i>or</i> <i>abemaciclib</i> of a severity necessitating permanent treatment withdrawal 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 prior to initiating treatment with this drug for this condition. AND            Patient must not develop disease progression while receiving treatment with this drug for this condition AND            Patient must have stable or responding disease AND            The treatment must be in combination with anastrozole or letrozole AND            The treatment must not be in combination with palbociclib <i>or</i> <i>abemaciclib</i> AND  <b>Patient must require dosage reduction requiring a pack of 21 tablets <sup>a</sup></b>  <b>Patient must require dosage reduction requiring a pack of 42 tablets <sup>b</sup></b></p>
<b>Population criteria:</b>	Patient must not be premenopausal.
<b>Prescriber Instructions</b>	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
<b>Caution</b>	QT monitoring is required for patients treated with this drug.

<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
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a Criterion only included in the restriction for 21 tablet pack

b Criterion only included in the restriction for 42 tablet pack

## 14 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.

## 15 Sponsor's Comment

The sponsor had no comment.