

6.01 ABEMACICLIB, Tablet 50mg, 100mg, 150mg, Verzenio[®], Eli Lilly Australia Pty Ltd

1 Purpose of submission

1.1 The submission requested extension to the current Section 85 (General Schedule) Authority Required (Telephone/Online) listing of abemaciclib to include use in combination with fulvestrant, for the treatment of non-premenopausal patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) inoperable locally advanced or metastatic breast cancer (mBC). The PBAC has not previously considered the combination of abemaciclib and fulvestrant for the proposed indication.

1.2 The submission presented a cost-minimisation analysis (CMA) versus ribociclib.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Non-premenopausal patients with inoperable HR+/HER2- mBC who have: <ul style="list-style-type: none"> Received previous endocrine therapy in the (neo)adjuvant or advanced/metastatic setting; and Experienced disease progression; and Developed endocrine resistance; and Not previously been treated with a CDK4/6 inhibitor or who developed an intolerance to an alternative CDK4&6 inhibitor necessitating withdrawal; and Have WHO ECOG status ≤2
Intervention	Abemaciclib (150 mg PO BD continuously) + Fulvestrant (500 mg IM on days 1, 15 and 28, then 4-weekly)
Comparator	Main comparator: ribociclib (600 mg PO QD, 3 weeks on 1 week off) + Fulvestrant (500 mg IM on days 1, 15 and 28, then 4-weekly);
Outcomes	Primary outcome: Progression free survival (PFS) Secondary outcomes: Overall survival (OS), Objective Response Rate (ORR), Health related quality of life (HRQoL), Safety
Clinical claim	In non-premenopausal patients with inoperable HR+/HER2- mBC, abemaciclib plus fulvestrant is clinically equivalent to ribociclib and fulvestrant in terms of comparative effectiveness and has non-inferior safety

BD = twice daily; ECOG = Eastern Cooperative Oncology Group; HR+= hormone receptor positive; HER2- = human epidermal growth factor receptor 2-negative; IM= intramuscular; mg=milligram; NSAI= non-steroidal aromatase inhibitor; po= per oral; QD = once daily; WHO = World Health Organisation.

Source: Table 1-1, p25 of the submission.

2 Background

Registration status

2.1 Abemaciclib was approved by the TGA in April 2019 for the following indication:

“VERZENIO is indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy or following prior endocrine therapy.

In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.”

- 2.2 Fulvestrant monotherapy (Faslodex) was TGA-approved in March 2006 for the treatment of postmenopausal women with HR+ advanced/metastatic breast cancer with progressive disease following prior tamoxifen therapy. A number of generic brands were TGA registered in 2020 including Fulvestrant Accord, Fulvestrant Intas and Fulvestrant Sandoz.

Previous PBAC consideration

- 2.3 The PBAC recommended listing ribociclib, in combination with fulvestrant, for the treatment of patients with HR+, HER2- unresectable advanced or metastatic breast cancer at its November 2020 meeting. The PBAC recommended ribociclib + fulvestrant based on a weighted price derived from a:

- cost minimisation analysis, based on ribociclib + fulvestrant compared with ribociclib + NSAI as first line treatment in the metastatic setting (i.e. including patients with de novo metastatic disease and those who received endocrine therapy in the (neo)adjuvant setting); and a
- cost-effectiveness analysis, based on ribociclib + fulvestrant versus everolimus + exemestane in second/subsequent line treatment

Overall, in its November 2020 consideration of ribociclib + fulvestrant “the PBAC considered the prices proposed in each of the settings were reasonable, and the resubmission’s overall proposal of a price that is the same as the current price for use in combination with NSAIs was appropriate”. (para 5.9, ribociclib Public Summary Document (PSD), November 2020 PBAC meeting). At the time of PBAC consideration, ribociclib was not PBS-listed for this combination.

- 2.4 The PBAC recommended listing fulvestrant for the treatment of patients with HR+, HER2- unresectable advanced or metastatic breast cancer at its July 2020 meeting. The PBAC considered that the proposed listing for fulvestrant as monotherapy “would not specifically prohibit use in combination with other medicines, such as CDK4/6 inhibitors and this use would be consistent with the TGA indications for some CDK4/6 inhibitors. However, such use is prohibited in the current CDK4/6 inhibitor restrictions, which state ‘treatment must be in combination with anastrozole or letrozole’ (paragraph 7.4, Fulvestrant PSD, July 2020 PBAC meeting). At the time of PBAC consideration, fulvestrant (as combination therapy or as monotherapy) was not PBS-listed for any indication.

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

3 Requested listing

Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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Table 2: Details of proposed PBS listing and criteria

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Dispensed Price for Max. Qty	Available brands
ABEMACICLIB						
abemaciclib 150 mg tablet, 56	11868P	1	56	5	\$5,542.46 (published)*	Verzenio
abemaciclib 100 mg tablet, 56	11871T	1	56	5	\$5,542.46 (published)*	Verzenio
abemaciclib 50 mg tablet, 56	11876C	1	56	5	\$5,542.46 (published)*	Verzenio
* The proposed published price is based on the current published price for ribociclib						
Restriction Summary 10039 / ToC: 10032						
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia						
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicessaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.						
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.						
Administrative Advice: No increase in the maximum number of repeats may be authorised.						
Administrative Advice: Special Pricing Arrangements apply.						
Indication: Locally advanced or metastatic breast cancer						
Treatment Phase: Initial treatment						
Clinical criteria: The condition must have endocrine resistance as demonstrated by progression of disease during or after treatment with an endocrine therapy.						
AND						
Clinical criteria: Patient must not have previously been treated with palbociclib or ribociclib or abemaciclib; or Patient must be untreated with each of: (i) abemaciclib, (ii) palbociclib, (iii) ribociclib; or Patient must have developed an intolerance to palbociclib or ribociclib of a severity necessitating permanent treatment withdrawal						
AND						
Clinical criteria: Patient must not have previously been treated with fulvestrant,						
AND						
Clinical criteria: The condition must be hormone receptor positive						
AND						
Clinical criteria: The condition must be human epidermal growth factor receptor 2 (HER2) negative						
AND						
Clinical criteria: The condition must be inoperable						
AND						
Clinical criteria: Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less						
AND						
Treatment criteria: Patient must not have previously received PBS-subsidised treatment with this drug for this condition,						
AND						

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Treatment criteria:
The treatment must be in combination with fulvestrant,
AND
Clinical criteria:
The treatment must be in combination with anastrozole or letrozole
<i>The treatment must be in combination, where the patient has never been treated with endocrine therapy for advanced/metastatic disease, with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant; or</i>
<i>The treatment must be in combination, where the patient has recurrence/progressive disease despite being treated with endocrine therapy for advanced/metastatic disease, with fulvestrant only</i>
Clinical criteria:
The treatment must not be in combination with palbociclib or ribociclib.
Population criteria:
Patient must not be premenopausal
Restriction Summary 10050 / ToC: 10019
Administrative Advice:
<i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Locally advanced or metastatic breast cancer
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not develop disease progression while receiving treatment with this drug for this condition
Patient must not have developed disease progression while being treated with this drug for this condition
AND
Clinical criteria:
Patient must have stable or responding disease
AND
Clinical criteria:
The treatment must be in combination with fulvestrant,
AND
Clinical criteria:
The treatment must be in combination with anastrozole or letrozole
<i>The treatment must be in combination with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant</i>
AND
Clinical criteria:
The treatment must not be in combination with palbociclib or ribociclib
AND
Population criteria:
Patient must not be premenopausal
Prescribing Instructions:
A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
Add Restriction Summary: NEW / ToC: NEW
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)

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Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
Administrative Advice: Patients 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.
Indication: Locally advanced or metastatic breast cancer
Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - 'Grandfather' treatment
Clinical criteria:
Patient must have received non-PBS-subsidised treatment with this drug for this PBS-indication prior to [insert date of PBS listing]
AND
Clinical criteria:
Patient must not have developed disease progression while being treated with this drug for this condition
AND
Clinical criteria:
Patient must have stable or responding disease
AND
Clinical criteria:
Patient must have been untreated with each of: (i) abemaciclib, (ii) palbociclib, (iii) ribociclib, at the time non-PBS supply was initiated; or Patient must have developed an intolerance to palbociclib or ribociclib of a severity necessitating permanent treatment withdrawal
AND
Clinical criteria:
The condition must be hormone receptor positive
AND
Clinical criteria:
The condition must be human epidermal growth factor receptor 2 (HER2) negative
AND
Clinical criteria:
The condition must be inoperable
AND
Clinical criteria:
Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 2 at the time of non-PBS supply was initiated
AND
Treatment criteria:
The treatment must be in combination with fulvestrant,
Clinical criteria:
The treatment must be in combination with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant, where the patient had never been treated with endocrine therapy for advanced/metastatic disease at the time non-PBS supply was initiated; or The treatment must be in combination with fulvestrant only, where at the time non-PBS supply was initiated, the patient had recurrent/progressive disease despite being treated with endocrine therapy for advanced/metastatic disease
AND
Clinical criteria:
The treatment must not be in combination with palbociclib or ribociclib
AND
Population criteria:
Patient must not be premenopausal
Prescribing Instructions:
A patient who has progressive disease when treated with this drug is no longer eligible for PBS subsidised treatment with this drug.

- 3.1 The proposed restrictions aligned with the clinical data in the pivotal study MONARCH-2 and are narrower than the approved TGA indication as the TGA indication allows use as the initial endocrine-based therapy, while the proposed PBS listing requires patients to have received prior endocrine-based therapy (and be endocrine-resistant). The submission noted that “some modification may be required [to the restriction] based on the detailed recommendations from the PBACs consideration of RIB+FUL and FUL at the July and November 2020 meetings”.
- 3.2 The proposed population is narrower than the population recommended for the listing of ribociclib plus fulvestrant at the November 2020 PBAC meeting, which also included patients without prior endocrine therapy. Unlike the MONALEESA-3 study (in ribociclib + fulvestrant), the patient population in the MONARCH-2 study (abemaciclib + fulvestrant) excluded untreated patients with de novo metastatic disease following an early protocol amendment. Therefore, there is only limited evidence from a post hoc exploratory analysis of 44 patients enrolled prior to that amendment to inform treatment with abemaciclib plus fulvestrant in this population. The ESC considered that use of CDKI+fulvestrant may be minimal in de novo patients as these patients would likely prefer an oral NSAID than IM injections of fulvestrant. The PBAC previously considered that the key clinical need for this combination in the first-line metastatic setting was for patients who relapse on or within 12 months of prior (neo)adjuvant treatment with an aromatase inhibitor for early breast cancer (i.e. a group of patients who are included in the requested restriction), rather than in the de novo population (para 7.3, Ribociclib Public Summary Document, July 2020 PBAC Meeting). The PBAC considered that a combined listing, including de novo metastatic patients, consistent with that recommended for ribociclib at the November 2020 PBAC meeting, would be appropriate for abemaciclib.
- 3.3 The submission proposed that the extension to the PBS listing be enabled through the addition of new item codes for each dose form, with restriction criteria that are separate and independent of the existing abemaciclib items (11868P, 11871T, 11876C). The Secretariat advised that this would be inconsistent with the recommended listing of ribociclib from the November 2020 PBAC meeting.
- 3.4 Grandfathering was proposed to accommodate 50-70 patients that will be enrolled to an early access program.
- 3.5 The submission requested that the Special Pricing Arrangement (SPA) pertaining to the current abemaciclib listing be applied to the extended listing. The submission did not request a specific effective price. A cost-minimisation price against ribociclib was requested and would be finalised when the effective ribociclib price is made available.

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

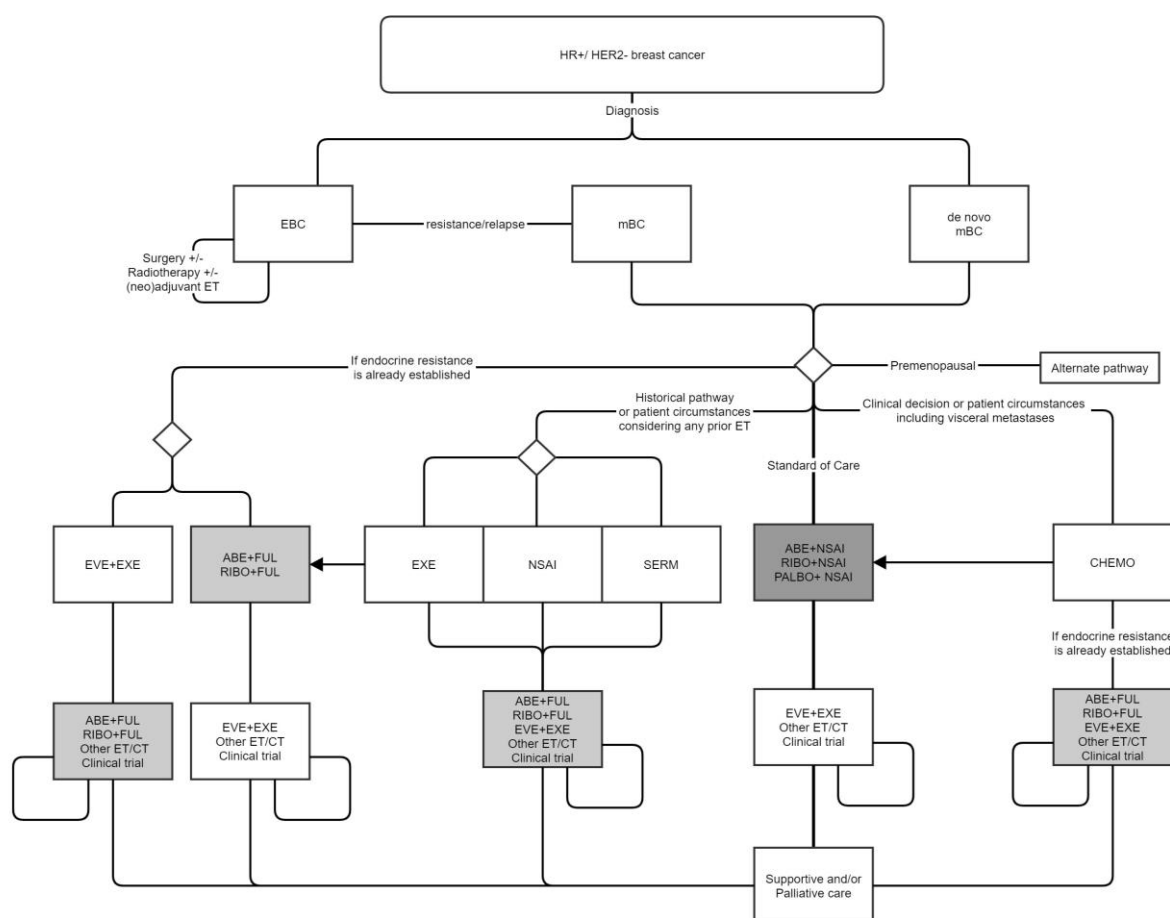
4 Population and disease

- 4.1 The disease and target population in the submission was similar to that presented for ribociclib in combination with fulvestrant at the July 2020 PBAC meeting i.e. patients

with HR+ and HER2- mBC who have received previous endocrine therapies in either the (neo)adjuvant or advanced metastatic treatment settings, experienced disease progression and developed endocrine resistance, and remain CDK 4&6i naïve. The recommended restriction for ribociclib + fulvestrant included treatment of patients who present with de-novo advanced/metastatic disease (treatment naïve) (para 3.5, Ribociclib PSD, November 2020 PBAC meeting). The clinical algorithm presented in the submission (Figure 1) reflected Australian clinical practice and was similar to that has been previously considered by PBAC for abemaciclib plus non-steroidal aromatase inhibitor.

- 4.2 Abemaciclib is a cyclin D-dependent kinases (CDK) 4 and 6 inhibitor.
- 4.3 For those patients who have experienced disease progression in the adjuvant setting, abemaciclib plus fulvestrant was proposed as first-line endocrine therapy in the metastatic setting, which would replace other PBS-listed abemaciclib or ribociclib combination regimens, voiding subsequent usage of CDKIs. PBS-listing of abemaciclib plus fulvestrant would also displace regimens such as everolimus and exemestane or chemotherapy or clinical trial participation as a subsequent line of therapy, potentially to second-line or third-line depending on when the abemaciclib plus fulvestrant is introduced in the clinical management of the patients. This was reflected in the post-discontinuation therapies in the MONARCH-2 clinical trial. It is unlikely to alter substantially the treatment options offered as later lines of therapy, although fewer patients may seek or be able to continue therapy as their disease progresses.

Figure 1: Summary of Australian clinical management algorithm for HR+/HER2- metastatic breast cancer, including current (dark grey) and proposed (light grey) placement of abemaciclib.



Source: Figure 1-1, p31 of the submission

Abbreviations: HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; EBC = early breast cancer; mBC = advanced or metastatic breast cancer; NSAI = non-steroidal aromatase inhibitor (letrozole or anastrozole); SERM = selective estrogen receptor modulator (tamoxifen); EXE = exemestane; EVE = everolimus; FUL = Fulvestrant; CDK 4&6 = cyclin dependent kinase 4&6 inhibitor (abemaciclib, ribociclib, palbociclib); ABE = abemaciclib; CHEMO = chemotherapy (any); ET = endocrine therapy (any)

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

5 Comparator

5.1 The submission nominated ribociclib in combination with fulvestrant as the main comparator. The submission noted that ribociclib was a close pharmacological analogue to abemaciclib, and the submission had a similar target population to that proposed for abemaciclib in combination with fulvestrant. This was reasonable.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described that treatment with abemaciclib improved quality of life and reduced the risk of disease recurrence and, although there are side effects such as hair thinning, diarrhoea and fatigue, abemaciclib was considered more tolerable than chemotherapy.
- 6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) supporting the submission for abemaciclib in combination with fulvestrant. The PBAC specifically noted the advice that the use of abemaciclib may provide more treatment options for patients diagnosed with metastatic disease. The BCNA also noted that treatment with abemaciclib was less likely than ribociclib to result in cardiac issues and neutropenia and may be preferred by patients with heart problems or bone disease and marrow compromise.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the abemaciclib submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the MONARCH-2 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for abemaciclib in combination with fulvestrant, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison of PFS and OS with fulvestrant + placebo.

Clinical trials

- 6.5 No direct randomised trials were available to inform the comparison. Key trials presented in the submission included:
- MONARCH-2, A randomised, double-blind, placebo-controlled, Phase 3 study of fulvestrant with or without abemaciclib, a CDK4&6 inhibitor, for women with HR+/HER2- locally advanced or metastatic breast cancer.
 - MONALEESA-3, A randomised, double-blind, placebo-controlled, Phase 3 study of ribociclib and fulvestrant in HR+/HER2- advanced breast cancer.
- 6.6 Details of the trials presented in the submission are provided in the table below.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<p>MONARCH-2 NCT02107703 I3Y-MC-JPBL</p>	<p>MONARCH 2: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer.</p> <p>Sledge, G. W., Toi, M. et al. 2017. "MONARCH 2: abemaciclib in Combination with Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy."</p> <p>Sledge, G. W., Toi, M. et al. 2019. "The Effect of Abemaciclib plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy - MONARCH 2: A Randomized Clinical Trial."</p>	<p>JPBL Clinical Study Report 2 May 2017 JPBL Clinical Study Report Addendum for the Interim Overall Survival Analysis September 2019</p> <p>J Clin Oncol 2015 35 (25):2875-2884.</p> <p>JAMA Oncol. 2020;6(1):116-124. doi:10.1001/jamaoncol.2019.4782 Published online September 29, 2019.</p>
<p>MONALEESA-3 NCT02422615</p>	<p>Slamon, D. J., Neven, P. et al. 2018. "Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3."</p> <p>Slamon, D. J., Neven, P. et al. 2020. "Overall Survival with RIB+FUL in Advanced Breast Cancer." The New England journal of medicine 382 (6):514-524.</p> <p>Beck JT, Neven P et al. 2019. "Patient-reported outcomes with ribociclib-based therapy in hormone receptor-positive, HER2-negative advanced breast cancer: results from the phase III MONALEESA-3, -3, and-7 trials."</p>	<p>Journal of Clinical Oncology 36 (24):2465-2472.</p> <p>NEJM 382 (6):514-524.</p> <p>DOI: 10.1158/1538-7445.SABCS18-P6-18-14 Published February 2019</p>

Source: Table 2-4, 43 of the submission, reproduced in part.

6.7 The key features of the randomised trials are summarised in the table below in the submission.

Table 4: Key features of the included evidence – indirect comparison

Trial	N	Design / duration	Relevant comparison	Patient population	Available outcomes
Abemaciclib plus fulvestrant vs placebo plus fulvestrant					
MONARCH-2	669	P3, MC, R, DB	Abemaciclib + fulvestrant HD 500mg FUL HD 500	Acquired ET resistance: either during/≤12m of adjuvant ET (primary) OR >12m from adjuvant ET OR during 1L ET for de novo metastatic disease.	Primary: Inv-PFS Secondary: OS, ORR, DOR, CBR, QOL and safety.
Ribociclib plus fulvestrant vs fulvestrant					
MONALEESA-3	726	MC, R, DB	FUL HD 500mg + Ribociclib 600mg	De novo advanced BC, or relapsed >12m from completing (neo)adjuvant ET and no treatment for adv or met disease, OR relapsing on or within 12m from (neo)adjuvant ET and no treatment for adv or met disease (early relapse), or relapse >12 m from (neo)adjuvant therapy and after one line of ET for adv or met disease, OR adv or met at diagnosis that progressed after one line of ET with no prior (neo)adjuvant treatment for early disease.	Primary: PFS inv Secondary: OS, ORR and safety.

Source: Figure 2-5, p44 of the submission.

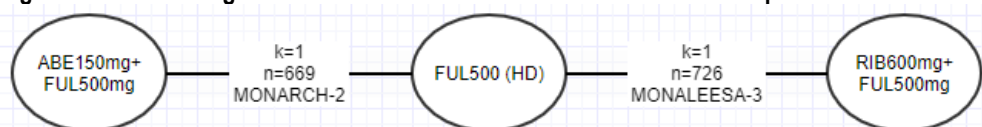
Abbreviations: P3=Phase 3; P2=Phase 2; MC=multi-centre; R=randomised; DB=Double blind; wk=week; LD=loading dose; HD=High dose; AD=Approved dose; OS=overall survival; PFS=progression-free survival; R=randomised; FUL HD=fulvestrant high dose; inv=investigator.

6.8 A key difference between the study designs is that the MONARCH-2 study examined the treatment effect of abemaciclib plus fulvestrant only in patients with varying degrees of endocrine resistance after patients with de novo metastatic disease were excluded from MONARCH-2 following an early protocol amendment; those already enrolled were not included in the ITT population for the primary efficacy analyses. Currently, there is only limited evidence from a post hoc exploratory analysis of 44 patients enrolled prior to that amendment to inform treatment with abemaciclib plus fulvestrant in this population. By comparison, those with de novo (newly diagnosed and previously untreated) metastatic disease were enrolled in MONALEESA-3 and are included in that study's ITT population. In the indirect comparison, the hazard ratios for ITT populations of both studies were compared, as well as the hazard ratios for the prespecified subgroup in MONALEESA-3 study of patients with endocrine resistance to inform a more comparable population with the ITT population in MONARCH-2. The listing for abemaciclib requested by the submission did not include this de novo population. As noted above, the ESC considered this that use of CDKI+fulvestrant would be minimal in de novo patients as these patients would likely prefer oral NSAI than intramuscular injections of fulvestrant.

6.9 Following a key protocol amendment, the starting dose for abemaciclib was lowered from 200mg twice daily to 150mg twice daily to improve tolerability. At this time, 121/441 patients were already enrolled, and all patients were required to switch to the lower dose. All patients were included in the safety study (a potential source of bias given the higher rates of discontinuation and dose reduction from the higher dose), and the sample size was expanded to ensure sufficient patients were enrolled at the lower starting dose to assess efficacy.

6.10 The two randomised clinical trials identified informed the indirect comparison with the common reference arm of placebo plus fulvestrant 500 mg.

Figure 2: Network diagram of the trials included to inform an indirect comparison



Source: Figure 2-2, p45 of the submission.

DB = double blind; MC = multi-centre; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised. FUL500= fulvestrant 500mg; ABE=abemaciclib; RIB=ribociclib.

Comparative effectiveness

6.11 Both trials met their primary efficacy endpoint, demonstrating a statistically significant improvement in PFS with the addition of either abemaciclib to fulvestrant (MONARCH-2) or ribociclib to fulvestrant (MONALEESA-3) compared with placebo plus fulvestrant (Table 5).

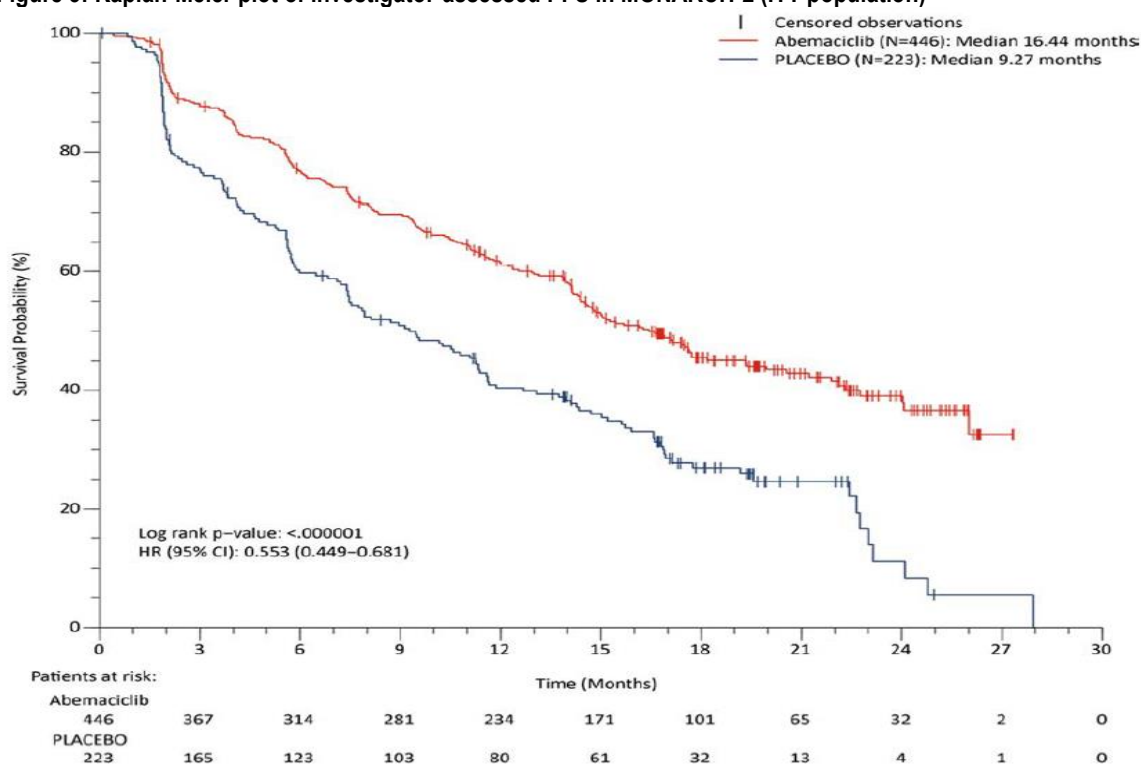
6.12 In MONARCH 2, the addition of abemaciclib to fulvestrant led to a statistically significant improvement in investigator-assessed median PFS of 7.1 months compared with placebo plus fulvestrant. The median PFS was 16.4 months versus 9.3 months (HR = 0.56 [95% CI:0.45, 0.68], $p < .0000001$), respectively. See Table 5 and Figure 3. PFS assessment based on a blinded independent radiological review was consistent with the investigator assessment.

Table 5: Results of PFS per investigator and OS in MONARCH-2 (ITT Population)

	ABE+FUL n/N (%)	PBO+FUL n/N (%)	Absolute difference	HR (95% CI)
Progression-free survival as primary PFS analysis at 14 February 2017				
Patients with event	222/446 (49.8%)	157/223 (70.4%)	20.6%	-
Median PFS months (95% CI)	16.4	9.3	7.1 months	0.55 [95% CI:0.45, 0.68], $p < 0.0000001$
Overall survival as at interim OS analysis at 20 June 2019				
Patients with event	211/466 (47 %)	127/223 (57%)	9.7%	-
Median months OS (95% CI)	46.7 (39.2, 52.2)	37.2 (34.36, 43.20)	9.5 months	0.757 (0.606, 0.945) $p = 0.014$

Source: Table JPBL.7.1., p19 of CSR Addendum

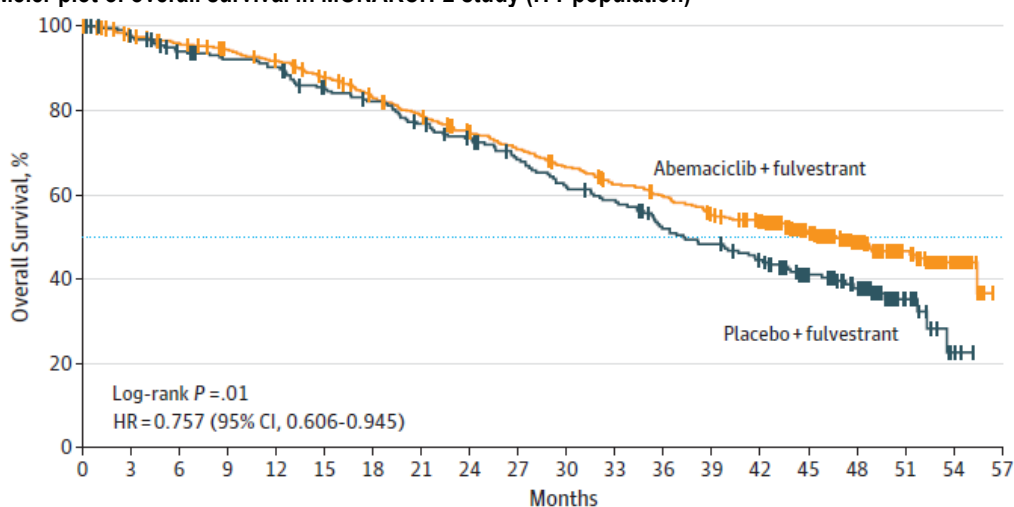
Figure 3: Kaplan-Meier plot of investigator-assessed PFS in MONARCH-2 (ITT population)



Source: Figure 2-5 of ES of the submission

6.13 Secondary efficacy endpoints of overall survival and objective response rates were also statistically significantly improved in MONARCH 2, with the addition of abemaciclib to fulvestrant, compared with fulvestrant alone: after median follow-up of 47 months, the risk of death was reduced by 24% (HR, 0.757; 95%CI, 0.606-0.945; P=0.01), and the median OS was improved by 9.5 months (47 months vs 37.3 months) (Figure 4). Subgroup analyses were consistent with the ITT analysis.

Figure 4: Kaplan-Meier plot of overall survival in MONARCH-2 study (ITT population)



No. at risk

Abemaciclib + fulvestrant	446	422	410	397	384	364	339	321	302	284	265	246	234	214	202	157	101	58	23	0
Placebo + fulvestrant	223	214	201	195	191	178	170	158	148	135	122	115	99	92	82	62	42	15	3	0

- 6.14 Objective response rates (mostly partial responses) in the MONARCH-2 study were increased two-fold with abemaciclib added to fulvestrant (35.2 % vs 16.1%).
- 6.15 Efficacy data do not appear to have been affected by the lowering of the initial starting dose, and the median duration of treatment at the higher dose was only 34 days.
- 6.16 The available quality of life data indicated a significant decrease in the quality of life domain assessing the impact of diarrhoea, but improvements in two other domains (pain and time to symptom development) with abemaciclib plus fulvestrant compared with fulvestrant alone.
- 6.17 Tables 6 and 7 present the indirect comparison of PFS by investigator assessment and OS, respectively from the MONARCH-2 and MONALEESA-3 studies. Updated PFS analyses (rather than data from the primary efficacy timepoint) and OS analyses were indirectly compared in the ITT populations of both studies. The main difference between the studies likely to influence the treatment effect, was the inclusion of patients with de novo metastatic disease in the MONALEESA-3 study due to their inherently better prognosis and treatment-responsiveness. This is addressed by a subsequent comparison between the prespecified subgroup of patients with endocrine-resistant disease in the MONALEESA-3 study (i.e. excluding those with endocrine therapy-naïve de novo metastatic disease in the MONALEESA-3), and the MONARCH-2 ITT population (all of whom had endocrine-resistant disease). The data used have been corrected to show the PFS at the time of prespecified analysis of the primary efficacy endpoint.

Table 6: Indirect comparisons of the primary endpoint, PFS - investigator assessed in MONARCH-2 (ITT Population) and MONALEESA-3 (ITT Population & Endocrine resistant subgroup) studies

Trial	Comparison	Test n/N (%)	Control n/N (%)	Test Median, Months (95% CI)	Control Median, Months (95% CI)	Hazard Ratio (95% CI) p-value
Progression free survival; ITT population						
MONARCH-2	ABE+FUL vs. PBO+FUL	297/446 (66.6)	193/223 (86.5)	16.9 [NR; NR]	9.3 [NR; NR]	0.54 [0.45; 0.64] <0.0001
MONALEESA-3	RIB+FUL vs. PBO+FUL	283/484 (58.5)	193/242 (79.8)	20.6 [NR; NR]	12.8 [NR; NR]	0.59 [0.49; 0.71] <0.0001
Indirect Comparison	ABE+FUL vs. RIB+FUL	-	-	-	-	0.91 [0.70; 1.18] 0.4724
Progression free survival; endocrine-resistant subgroup of MONALEESA-3 study, ITT population of MONARCH-2						
MONARCH-2	ABE+FUL vs. PBO+FUL	297/446 (66.6)	193/223 (86.5)	16.9 [NR; NR]	9.3 [NR; NR]	0.54 [0.45; 0.64] <0.0001
MONALEESA-3	RIB+FUL vs. PBO+FUL	167/237 (70.46)	95/109 (87.15)	14.6 [NR; NR]	9.1 [NR; NR]	0.57 [0.44; 0.74] <0.0001
Indirect Comparison	ABE+FUL vs. RIB+FUL	-	-	-	-	0.94 [0.68; 1.29] 0.7064

Source: Table 2-37, p111 of the submission.

Data cut-off date 3 June 2019 for MONALEESA-3; Data cut-off date June 20, 2019 MONARCH-2

No confidence intervals were provided in the submission for the updated median PFS or OS for MONARCH-2

Table 7: Indirect comparisons of the secondary endpoint, OS, investigator assessed in MONARCH-2 (ITT Population) and MONALEESA-3 (ITT Population & Endocrine resistant subgroup) studies.

Trial	Comparison	Test n/N (%)	Control n/N (%)	Test Median, Months (95% CI)	Control Median, Months (95% CI)	Hazard Ratio (95% CI) p-value
Overall survival; ITT population						
MONARCH-2	ABE+FUL vs. PBO+FUL	211/446 (47.3)	127/223 (57.0)	46.7 [NR; NR]	37.3 [NR; NR]	0.76 [0.61; 0.94] 0.0139
MONALEESA-3	RIB+FUL vs. PBO+FUL	167/484 (34.5)	108/242 (44.6)	NR [NR; NR]	40.0 [NR; NR]	0.72 [0.56; 0.92] 0.0086
Indirect Comparison	ABE+FUL vs. RIB+FUL	-	-	-	-	1.05 [0.76; 1.46] 0.7664
Overall survival; endocrine-resistant subgroup of MONALEESA-3 study, ITT population of MONARCH-2						
MONARCH-2	ABE+FUL vs. PBO+FUL	211/446 (47.3)	127/223 (57.0)	46.7 [NR; NR]	37.3 [NR; NR]	0.76 [0.61; 0.94]
MONALEESA-3	RIB+FUL vs. PBO+FUL	102/237 (43.03)	60/109 (55.04)	40.02 [NR; NR]	32.5 [37; NR]	0.73 [0.53; 1.00]
Indirect Comparison	ABE+FUL vs. RIB+FUL	-	-	-	-	1.04 [0.71; 1.52]

Source: Table 2-36, p111 of the submission.

Data cut-off date 3 June 2019 for MONALEESA-3; Data cut-off date June 20, 2019 MONARCH-2.

No confidence intervals were provided in the submission for the updated median PFS or OS for MONARCH-2

6.18 The submission did not specify a non-inferiority margin. The precedent of a non-inferiority margin of 1.4 was previously accepted by PBAC during consideration of

palbociclib (palbociclib PSD, March 2018 PBAC meeting, paragraph 5.11)² and abemaciclib (abemaciclib PSD, March 2019 PBAC meeting, paragraph 6.13) for use in conjunction with a non-steroidal aromatase inhibitor in a similar indication. The indirect comparison of PFS by investigator review results in a HR of 0.91 (95% CI: 0.7, 1.18; p=0.47). 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.

- 6.19 Although there was a shorter median PFS in both arms of the MONARCH-2 trial compared with the respective arms in the MONALEESA-3 study, the indirect comparison of PFS in the prespecified subgroup of patients with demonstrated endocrine-resistance showed a similar reduction in the risk of progression or death in both clinical trials: HR of 0.94 (95% CI: 0.68, 1.29; p=0.71). This supports that the difference in PFS is most likely explained by eligibility criteria requiring demonstrated endocrine-resistance in MONARCH-2, whereas the ITT population in the MONALEESA-3 study included patients with de novo metastatic disease, who have an intrinsically better prognosis and greater treatment-responsiveness.
- 6.20 Other subgroup analyses were consistent with the primary efficacy outcome within each study.

Comparative harms

- 6.21 The evaluation noted that the adverse event profiles of abemaciclib and ribociclib differ (making comparison of individual adverse event rates of limited value), that the safety data utilised in the analyses were for different durations of exposure and follow-up from the abemaciclib and ribociclib trials (likely to increase the rate of adverse events reported for ribociclib), and included the patients initially dosed at the higher dose of abemaciclib. This raised uncertainties about the use of indirect comparisons of events rates between the trials.
- 6.22 To improve tolerability, a protocol amendment lowered the initial starting dose for abemaciclib from 200mg twice daily to 150mg twice daily, after 121/441 patients commenced were already enrolled. All patients were required to switch to the lower dose. Adverse event rates were higher at the higher dose and their inclusion in the safety population has inflated the event rates including dose modifications and discontinuations. The median duration of treatment at the higher dose was only 34 days.

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 8: Summary of key adverse events in the MONARCH-2 (Safety population)

MONARCH-2 ^a	Abemaciclib plus fulvestrant N=441	Placebo plus fulvestrant N=223	RD
with ≥1 TEAE	435 (98.6)	199 (89.2)	9.4%
with ≥1 CTCAE with ≥Grade 3 TEAE ^b	276 (62.6)	53 (23.8)	38.8%
with ≥1 SAE	99 (22.4)	24 (10.8)	11.6%
Discontinued study treatment due to AE ^c	38 (8.6)	7 (3.1)	2.77%
Discontinued study treatment due to SAE ^c	18 (4.1)	3 (1.3)	5.5%
Death due to AE on study treatment ^d	6 (1.4)	1 (0.4)	1%
Death due to an AE within 30 days of discontinuing study treatment	3 (0.7)	1 (0.4)	+0.3%

Source: Source Table 2-22, p88 of the submission;

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; TEAE=treatment-emergent adverse event; CTCAE = Common Treatment Criteria for Adverse Event; AE= adverse event; SAE = serious adverse event.

a Patients may be counted in >1 category

b Includes events that were considered related to study treatment as judged by the investigator

c Patients who died on study treatment with primary cause as AE or SAE are also included as discontinuations.

d Deaths are also included as SAEs and discontinuations due to AEs.

- 6.23 The most common adverse reactions in the abemaciclib plus fulvestrant arm compared with the control arm of MONARCH 2 (incidence ≥20% in either arm and with ≥10% difference between the arms) were diarrhoea (87% vs 28%), neutropenia (50% vs 4%), nausea (49% vs 25%), fatigue (49% vs 25%), abdominal pain (37% vs 17%), anaemia (35% vs 4%), leukopenia (33 vs 2%), vomiting (29% vs 12%), decreased appetite (29% VS 14%). Grade 3 events occurring at ≥10% of patients in the abemaciclib arm included neutropenia (27%), diarrhoea (15%) and leukopenia (11%).
- 6.24 Adverse events (most commonly diarrhoea and neutropenia) leading to dose interruptions, dose reductions and treatment discontinuations (one or both study medications) occurred in 62%, 55% and 10.7% of patients, respectively. Reasons for discontinuation included adverse events (9%) and withdrawal by patient (6.3%).
- 6.25 Antidiarrhoeal medication were required per protocol and were taken by 69% of patients in the abemaciclib plus fulvestrant arm.
- 6.26 The most common adverse events in the ribociclib plus fulvestrant arm (incidence ≥20%) compared with the control arm of MONALEESA-3 were: neutropenia (70% vs 2.1%), nausea (45% vs 28%), fatigue (32% vs 33%), diarrhoea (29% vs 20%), leukopenia (28% vs 2%), vomiting (27% vs 13%), constipation (25% vs 12%), arthralgia (24% vs 27%), cough (22% vs 15%) and headache (22% vs 20%).
- 6.27 Compared with ribociclib plus fulvestrant, fewer patients treated with abemaciclib plus fulvestrant experienced neutropenia (any grade) or leukopenia, or QT prolongation. However, these patients were more likely to experience diarrhoea, and anaemia, and events of neutropenia and leukopenia were still common and required dose modifications. Discontinuations from either study occurred at similar rates, and for abemaciclib were due to adverse events in 10.7% of patients and a further 6.3% of patients withdrew from treatment in the MONARCH-2 study. Infections and abnormal liver function tests occurred at similar rates in both arms of the MONARCH-2 study.

Benefits/harms

6.28 The indirect comparison presented in the submission supported the claim of non-inferiority of efficacy for abemaciclib compared with ribociclib but did not allow for a meaningful quantitative comparison of the harms of abemaciclib and ribociclib due to the differing side effect profiles, and the impact of the higher initial abemaciclib starting dose on dose reductions and discontinuations. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.29 The submission described abemaciclib as non-inferior in terms of effectiveness compared with ribociclib. This claim was adequately supported by the clinical data provided in the submission.

6.30 The submission described abemaciclib as non-inferior in terms of safety compared with ribociclib. The following issues were identified:

- Data were presented from different durations of follow-up for the two trials, favouring the abemaciclib arm.
- 121/441 (27%) patients in the safety population in the abemaciclib arm commenced at a higher dose no longer recommended, resulting in higher rates of adverse events, dose modifications and discontinuations – this favours the ribociclib arm.

6.31 The PBAC considered that abemaciclib + NSAI was non-inferior in terms of comparative effectiveness and safety compared with ribociclib + NSAI while noting there were differences between the safety profiles of abemaciclib and ribociclib.

Economic analysis

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

6.33 In the submission, the equi-effective doses were estimated as:

- abemaciclib 273.10 mg/day (based on a median relative dose intensity (RDI) of 90.1%) for 28 days every 28-day cycle is equivalent to
- ribociclib 552.6 mg/day (based on a median RDI 92.1%) for 21 days every 28-days.

6.34 The dose intensities were based on the doses reported in MONARCH-2 and MONALEESA-3. The submission stated that median RDIs were used as the mean RDI was not publicly available for MONALEESA-3. However, the PBAC PSD for ribociclib from July 2020 (which would not have been publicly available at the time the submission was prepared) states that ‘the relative dose intensity of ribociclib when used with fulvestrant in the MONALEESA-3 trial’ was 85.2% (para 6.54, Ribociclib PSD, July 2020 PBAC meeting).

- 6.35 The Pre-Sub-Committee Response (PSCR) incorporated the mean dose intensities into a revised cost-minimisation analysis (also corrected for an error, as outlined in the Table 9 footnote). Thus, the revised equi-effective doses proposed in the PSCR were:
- abemaciclib 260.7 mg/day (based on a mean RDI of 86.9%) for 28 days every 28-day cycle is equivalent to
 - ribociclib 511.2 mg/day (based on a mean RDI 85.2%) for 21 days every 28-days.
- 6.36 The evaluation considered that it may have been more appropriate to use the dose intensities that were used to calculate the equi-effective doses of abemaciclib versus ribociclib in its existing listing, i.e. for use in combination with a non-steroidal aromatase inhibitor (NSAI) i.e. anastrozole or letrozole because:
- It is unclear whether the dose intensity of CDK inhibitors would be likely to change when administered with fulvestrant rather than with an NSAI. In its July 2020 consideration of ribociclib + fulvestrant in the first-line setting, which was cost-minimised to ribociclib + NSAI, the ESC considered that “there did not appear to be a clinical reason why dose intensities for ribociclib would differ depending on its combination with fulvestrant or NSAI” (para 6.54, Ribociclib PSD, July 2020 PBAC meeting). The cost-minimisation analysis applied the same relative dose intensity (85.2%) for ribociclib regardless of whether it was used in combination with fulvestrant or an NSAI, despite differences in ribociclib dose intensity having been reported in the trial of ribociclib + fulvestrant (MONALEESA-3) compared with the trial of ribociclib + an NSAI (MONALEESA-2) (para 6.54 and Table 12, Ribociclib PSD, July 2020 PBAC meeting).
 - The median dose intensities used in the submission were based on the ITT populations of the two trials, which may have transitivity issues given over 50% of patients in the MONALEESA-3 trial population had de novo disease, while no patients with de novo disease were included in the ITT population of MONARCH-2. Dose intensity data were not available for the endocrine-resistant subgroup in MONALEESA-3, which may have been more comparable to the MONARCH-2 ITT population.
- 6.37 The PSCR and pre-PBAC response did not agree that it would be appropriate to use the same dose intensities that were used to calculate the equi-effective doses of abemaciclib versus ribociclib in its existing listing. The PSCR and pre-PBAC response argued that the listings were based on different sources of evidence with a different concomitant therapy.
- 6.38 The submission did not include an adjustment for treatment duration. The median duration of treatment in the trials was 11.9 months for abemaciclib versus 15.8 months for ribociclib. The median duration of treatment was also shorter in the placebo arm of the abemaciclib trial (the median duration of treatment with placebo was 7.9 months in MONARCH-2 and 12.0 months in MONALEESA-3). Exclusion of the duration of treatment from the cost-minimisation analysis was appropriate given: the differences between the trial populations; it would be consistent with the claim of

non-inferior comparative effectiveness; and it would be consistent with the calculation of the equi-effective doses for the existing listing of abemaciclib. Taking into account a shorter duration of treatment with abemaciclib would result in a higher price for abemaciclib.

- 6.39 The submission claimed that abemaciclib would result in decreased use of ECG monitoring, which is required with ribociclib but not abemaciclib, and included a cost offset (resulting in a price advantage) for this. The submission assumed that patients treated with ribociclib would require three ECGs over the first 15 months of treatment, while patients treated with abemaciclib would not require any ECG monitoring. The submission estimated this would result in a reduction in the total cost per treatment cycle of \$5.49 for abemaciclib compared with ribociclib. The evaluation and the ESC considered this was not appropriate, as outlined in the three paragraphs below.
- 6.40 The submission acknowledged that abemaciclib is associated with higher rates of diarrhoea than ribociclib, but did not include any additional costs for the treatment of diarrhoea, stating that the cost impact would be minimal. The submission stated that limited amounts of loperamide are used through the PBS as it is generally cheaper for patients to purchase loperamide over-the-counter rather than via a PBS script.
- 6.41 However, in its March 2019 consideration of abemaciclib for its existing indication, 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” (para 10.7 Abemaciclib PSD, March 2019 PBAC meeting). The PBAC also “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” (para 7.9 Abemaciclib PSD, March 2019 PBAC meeting). Thus, no additional costs or cost offsets were included in the cost-minimisation analysis on which the existing price of abemaciclib is based (i.e. cost-offsets for reductions in ECG monitoring with abemaciclib were not included in the existing cost-minimisation analysis).
- 6.42 The revised analysis provided in the PSCR removed the ECG costs from the cost-minimisation calculations, which the ESC considered was appropriate.
- 6.43 The submission noted that there is a Special Pricing Arrangement (SPA) in place for ribociclib and thus the published ex-manufacturer price of \$5,360.50 (for 600mg/day dose) was used in the cost-minimisation analysis. The results of the revised cost-minimisation analysis presented in the PSCR are shown in the table below, including and excluding ECG costs.

Table 9: Results of the cost-minimisation analysis – updated to reflect the mean dose intensity per PSCR

Component	Abemaciclib	Ribociclib
Recommended Dose	300 mg daily (150 mg twice daily)	600 mg daily
Dose intensity (mean)	86.9%	85.2%
Dose (mg /day)	260.7 mg per day	511.2 mg per day
Treatment days per cycle	28 days of a 28-day cycle	21 days of a 28-day cycle
mg used per 28-day cycle	7,300 mg	10,735 mg
Including ECG cost offsets		
Cost offsets (ECG)	\$0	\$5.49
Cost per mg	\$0.626	\$0.425 ^a
Total: Average cost per patient per cycle	\$4,572	\$4,572
Revised analysis excluding ECG costs – per Table 2 of PSCR		
Cost offsets (ECG)	\$0	\$0
Cost per mg	\$0.626	\$0.425
Total: Average cost per patient per cycle	\$4,566	\$4,567

Source: Table 3-5 of the submission; Table 2 of the PSCR; calculated during evaluation using Attachment 4 - Cost Minimisation workbook (abemaciclib).xlsx.

^a The PSCR also corrected for an issue identified during evaluation. In the submission, the cost per mg of ribociclib was incorrectly based on the price of one pack (200 mg, quantity 63) divided by the mg used per 28-day cycle taking dose intensity into account, rather than the actual number of mg in a pack (i.e. in 'CMA, by cycle' worksheet, cell C18 should have been divided by 12,600 mg (actual dose in pack of 200 mg * 63 tablets) rather than by 11,605 mg (cell C17, which is the average dose used per cycle accounting for dose intensity). This is consistent with the methodology used in the agreed cost-minimisation analysis for the existing listing of abemaciclib.

6.44 The table below shows sensitivity analyses conducted during evaluation using the published prices. Note that the financial estimates use the 'average cost per patient per cycle' as a flat price for all dose strengths of abemaciclib.

Table 10: Sensitivity analyses conducted during evaluation

	Abemaciclib AEMP	
	Average cost per patient per cycle	Cost per mg
Revised base case excluding ECG costs	\$4,567	\$0.626
Dose intensity based on existing listing 79.2% for abemaciclib, 79.5% for ribociclib	\$4,261	\$0.641

Source: calculated during evaluation using Attachment 4 - Cost Minimisation workbook (abemaciclib).xlsx.

6.45 The PBAC considered that the price of abemaciclib, when used in combination with fulvestrant, should be no higher than the price for the existing listing in combination with an NSAID, which is consistent with its November 2020 consideration of ribociclib + fulvestrant where "the PBAC considered the prices proposed in each of the settings were reasonable, and the resubmission's overall proposal of a price that is the same as the current price for use in combination with NSAIDs was appropriate". (para 5.9, ribociclib PSD, November 2020 PBAC meeting).

Drug cost/patient/course

Table 11: Drug cost per patient for abemaciclib and ribociclib – based on revised prices in Table 2 of PSCR

	Abemaciclib Trial dose and duration	Abemaciclib CMA	Abemaciclib Financial estimates	Ribociclib Trial dose and duration	Ribociclib CMA	Ribociclib Financial estimates
Dose intensity	Mean: 86.9%	Mean: 86.9%	100% Compliance	Mean: 85.2%	Mean: 85.2%	Not considered
Mean dose	260.7 mg/day	260.7 mg/day	Not considered (Flat pricing across strengths)	511.2 mg/day for 21 days every 28-days	511.2 mg/day for 21 days every 28-days	Not considered
Duration	Trial mean: 18.9 cycles ^c	Not considered	13.04 cycles ^b	20.2 months ^d (21.9 cycles)	Not considered	Not considered
Cost/patient/ 28- day cycle	\$4,728 ^a	\$4,728 ^a	\$4,728 ^a	\$4,728 ^a	\$4,728 ^a	Not considered
Cost/patient/ course	\$89,357	Not calculated	\$61,652	\$103,541 ^c	Not calculated	Not considered

Source: Calculated during evaluation

^a Per Table 2 of PSCR, this is based on the mean dose intensity, excludes ECG monitoring costs, and is corrected for the calculation error noted in the economic analysis section.

^b Based on the (truncated) mean number of 'cycles received per patient' reported in the MONARCH-2 CSR (Sept 2019), Table JPBL.8.1, p31), noting that the trial is on-going with 17.3% of patients still on treatment with abemaciclib at the June 2019 data cut-off.

^c Based on para 7.22, ribociclib PSD, July 2020 PBAC meeting. This is not comparable with the abemaciclib duration reported in this table as the trials have different durations of follow-up and (per para 6.85, ribociclib PSD, July 2020 PBAC meeting) this was not based on the mean duration of treatment in the MONALEESA-3 trial

6.46 The figures in the table above were updated based on the revised prices in Table 2 of the PSCR (using mean dose intensities and excluding ECG costs) and are based on the published price of ribociclib.

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC.

6.48 The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the PBS listing of abemaciclib for non-premenopausal patients with HR+, HER2- advanced breast cancer.

6.49 Table 12, 13, 14 contains the key inputs for financial estimates.

Table 12: Data sources and parameter values applied in the utilisation and financial estimates for eligible population

Data	Value	Source	Comment
Eligible population			
Eligible Patients Population 1 (1L ER)	Yr 1: [redacted] ¹ Yr 2: [redacted] ² Yr 3: [redacted] ² Yr 4: [redacted] ² Yr 5: [redacted] ² Yr 6: [redacted] ²	Breast cancer incidence data from AIHW. The incidence of relapsed metastatic breast cancer the number of patients that are HR+/HER2 were based on PBAC and DUSC advice from previous palbociclib and abemaciclib submissions (Palbociclib PSD, Mar 2017; Abemaciclib PSD, Mar 2019). The proportion of endocrine resistance was estimated at 30% based on D'Souza et al 2018 and proportion of chemotherapy use was based on data from the IPSOS Australia Oncology monitor 2020 and Cardoso 2020 which reported 25% of patients using chemotherapy as first line.	The use of the AIHW data appears to be reasonable. The proportion of endocrine resistance reported by D'Souza et al 2018 is based on a study from 2005 and it is uncertain whether this statistic is still appropriate given the changes in clinical practice in the last fifteen years. The proportion of chemotherapy use was unable to be verified during evaluation from the sources provided in the submission.
Eligible Patients Population 2 (2L ER Post EVE+EXE)	Yr 1: [redacted] ¹ Yr 2: [redacted] ¹ Yr 3: [redacted] ¹ Yr 4: [redacted] ¹ Yr 5: [redacted] ¹ Yr 6: [redacted] ¹	Eligible second line post EVE+EXE patients were obtained by using the previously calculated first line population and assuming the patients who did not have treatment as first line went on to use EVE+EXE and a proportion of these patients would have this treatment second line (Attachment 5 of the main submission).	This population is overestimated as DUSC has previously advised the utilisation of everolimus for breast cancer has been declining with approximately 85 prevalent patients supplied everolimus through the PBS as at March 2020 based on approved Authorities data from Services Australia (Ribociclib PSD, July 2020, para 6.87).
Eligible Patients Population 3 (2L ES Post AI/SERM)	Yr 1: [redacted] ¹ Yr 2: [redacted] ¹ Yr 3: [redacted] ¹ Yr 4: [redacted] ¹ Yr 5: [redacted] ¹ Yr 6: [redacted] ¹	Eligible second line post AI/SERM patients were obtained by using the previously calculated total HR+/HER2-NPM MBC and multiplying that by the proportion of patients not receiving CT are ES and not choosing a CDKi+AI and who go on for further treatment (Attachment 5 of the main submission)	Likely overestimated as PBAC considered the use of CDKi's in the second line setting will be limited to prevalent patients who began treatment with AI monotherapy prior to the listing of a CDKi+NSAI and that this population would be relatively small (Ribociclib PSD, July 2020, para 7.19)
Eligible Patients Population 4 (2L post CT)	Yr 1: [redacted] ¹ Yr 2: [redacted] ¹ Yr 3: [redacted] ¹ Yr 4: [redacted] ¹ Yr 5: [redacted] ² Yr 6: [redacted] ²	Eligible second line post CT patients were obtained by using the previously calculated total HR+/HER2- NPM MBC and multiplying that by the proportion of patients receiving CT and who go on for further treatment (Attachment 5 of the main submission)	Likely overestimated as DUSC noted 'there is no evidence to suggest that RIBO+FULV is more effective in treating visceral disease than RIBO+NSAI, and therefore neither protocol is likely to displace chemotherapy' (Ribociclib PSD, July 2020 para 6.88).

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

Table 13: Data sources and parameter values applied in the utilisation and financial estimates for treatment utilisation

Data	Value	Source	Comment
Treatment utilisation			
Uptake rate for all populations	Yr 1: 60% Yr 2: 70% Yr 3: 80% Yr 4: 90% Yr 5: 90% Yr 6: 90%	Assumptions (Attachment 5 of the main submission)	These assumptions were not justified by the submission and are likely to overestimate the treated populations particularly in Population 4.
Treatment Duration	12 months	Median duration of therapy was approximately 12 months in MONARCH-2 (Sledge et al 2017)	The results from the MONARCH-2 trial reported in Sledge et al 2017 indicate the median duration of treatment was approximately 12 months. The follow-up results in Sledge et al 2019 indicate the mean treatment duration is 18.9 cycles or approximately 17 months. The most recent data would be more appropriate to estimate the time on abemaciclib.
Scripts dispensed	Yr 1: [redacted] Yr 2: [redacted] Yr 3: [redacted] Yr 4: [redacted] Yr 5: [redacted] Yr 6: [redacted]	Calculated based on number of patients treated at 13.04 packs per year with 100% compliance divided by two due to the assumption of sharing the market evenly with ribociclib.	The number of scripts dispensed per year is uncertain. The follow-up data for MONARCH-2 indicates time on abemaciclib will be greater than 12 months. As such, the use of a 12 month treatment duration underestimates the utilisation of scripts following year 1 of the estimates as there is no continuation on treatment after initiation into subsequent years of the forward estimates. The assumption of 100% compliance in medications which are taken twice (abemaciclib) and three times a day (ribociclib) is overestimated which overestimates the total number of scripts dispensed. It is unclear whether the market will also be shared evenly due to the different adverse effect profiles of ribociclib and abemaciclib.

The redacted values correspond to the following ranges:
¹ 5,000 to < 10,000

Table 14: Data sources and parameter values applied in the utilisation and financial estimates for drug costs

Data	Value	Source	Comment
Costs			
Proposed medicine			
Abemaciclib all strengths	\$5,365.50	Requested price, based on the average cost per patient per cycle in the cost-minimisation analysis. Table 2 of the PSCR updated this to be an AEMP of \$4,566.73 (without ECG costs), which equates to a DPMQ of \$4,728.	Higher than current listing of abemaciclib, based on PSCR updates
Comparator			
Ribociclib 200mg, 63	\$5,360.50	Ribociclib PBS item 11386G	Based on current published DPMQ
Ribociclib 200mg, 42	\$3,734.50	Ribociclib PBS item 11397W	Based on current published DPMQ
Ribociclib 200mg, 21	\$1939.87	Ribociclib PBS item 11385F	Based on current published DPMQ
Patient copayment	\$20.56 PBS \$4.95 RPBS	PBS statistics for ribociclib item code 11386G, 11398W, 11385F	
MBS costs	\$27.45	Reduced usage of MBS item 11704 which is twelve-lead electrocardiography needed for regular monitoring with ribociclib usage	This seems reasonable.

Source: Table 4-2, Table 4-3, Table 4-4, Attachment 5 – Cost and utilisation workbook (abemaciclib).
 Note: HR+/HER2-=Hormone Receptor positive/HER2 negative, NPM=non-premenopausal, MBC= Metastatic breast cancer, ER=endocrine resistant, EVE=everolimus, EXE= exemestane, ES= endocrine sensitive, AI= aromatase inhibitor, SERM= selective oestrogen receptor modulator, CDKi=cyclin-dependant kinase inhibitor (such as ribociclib, abemaciclib or palbociclib), CT=chemotherapy.

6.50 Table 15 presents the estimated use and financial implications.

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Table 15: Estimated use and financial implications

Year	2021	2022	2023	2024	2025	2026
Eligible patients						
Population 1 (1L ER)	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ²
Population 2 (2L ER post EVE+EXE)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Population 3 (2L ES post AI/SERM)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Population 4 (2L post CT)	█ ¹	█ ¹	█ ¹	█ ¹	█ ²	█ ²
Total eligible patients (populations 1 to 4)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Treated patients^b						
Population 1 (1L ER)	█ ¹	█ ¹	█ ¹	█ ²	█ ²	█ ²
Population 2 (2L ER post EVE+EXE)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Population 3 (2L ES post AI/SERM)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Population 4 (2L post CT)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total receiving ABE (populations 1 to 4)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Total PBS/RPBS packs						
ABE - All ^a	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
RIB – All	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to the PBS/RPBS (published price and excluding patient copayments)						
PBS						
New listing	-\$ █ ⁴	-\$ █ ⁴	-\$ █ ⁴	-\$ █ ⁵	-\$ █ ⁵	-\$ █ ⁵
Changed listing	-\$ █ ⁴	-\$ █ ⁶	-\$ █ ⁴	-\$ █ ⁴	-\$ █ ⁴	-\$ █ ⁴
Net impact	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷
RPBS						
New listing	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷
Changed listing	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷
Net impact	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷
PBS/RPBS						
Net impact	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷
Using price from the PSCR's revised cost-minimisation analysis (per Table 2 of PSCR)						
Net impact to PBS/RPBS ^c	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷	-\$ █ ⁷

Source: Table 4-4 of submission, Table 4-5 of submission, Table 4-6 of submission

^a Calculated based on number of patients treated at 13.04 packs per year with 100% compliance divided by two due to the assumption of sharing the market evenly with ribociclib

^b Calculated during the evaluation based on the treatment uptake rates proposed in the submission for each population

^c Also incorporates revised mark-ups that were effective from 1 January 2021 (i.e. revised wholesale mark-up). For abemaciclib, this results in a DPMQ of \$4,727.89, based on the average cost per patient per cycle of \$4,567 per Table 2 of the PSCR, which excludes ECG costs (use of the 'average cost per patient per cycle' in the financial estimates was consistent with the submission's approach). This DPMQ also assumes community pharmacy dispensing (consistent with the submission's approach). The ribociclib DPMQ was also updated to reflect the January 2021 mark-ups.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ \$30 million to < \$40 million

⁵ \$40 million to < \$50 million

⁶ \$20 million to < \$30 million

⁷ \$0 to < \$10 million

- 6.51 Based on the revised abemaciclib price proposed in the PSCR, the net impact to the PBS/RPBS of listing abemaciclib was estimated to be a net cost saving in Year 6 and a total net cost saving in the first 6 years of listing.
- 6.52 In its March 2019 consideration of abemaciclib (for use in combination with an NSAID), 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' (para 12.7, Abemaciclib, PSD, March 2019 PBAC meeting).
- 6.53 The estimated eligible populations for abemaciclib are likely to be overestimated. The assumptions to derive the first line eligible population are based on non-contemporary data for the proportion of patients with endocrine resistance, and the proportion of patients using chemotherapy could not be verified during the evaluation. Several parameters used to forecast the second line population, including prior use of EVE+EXE, AI/SERM and chemotherapy, were overestimated. The assumptions for the uptake of abemaciclib in all populations was not adequately justified in the submission.
- 6.54 Population One: The evaluation considered it was unclear whether initiating patients who would be treated with a CDKi+AI (i.e. pathway three in the submission) would want a parenteral treatment option (i.e. pathway one) over an oral treatment.
- 6.55 Population Two: The estimates for this population are overestimated. DUSC has previously advised in its consideration of ribociclib that the utilisation of everolimus for breast cancer has been declining with approximately 85 prevalent patients as at March 2020 based on approved Authorities data from Services Australia (para. 6.87, Ribociclib, PSD, July 2020; data provided by the DUSC Secretariat).
- 6.56 Population Three: The uptake rate in this population is overestimated. The uptake is likely to be low in this setting and would likely reduce over time based on reducing utilisation of the therapy in clinical practice.
- 6.57 Population Four: The proportion of patients moving on to treatment with a CDKi+fulvestrant following chemotherapy is likely to be very small. There is however likely to be a small population that may be endocrine resistant who could be considered as suitable for this treatment given the different mode of action of fulvestrant. The uptake rate for this population would likely be considerably smaller.
- 6.58 The assumption of full treatment compliance for all populations is unlikely to be realised in practice.
- 6.59 The average duration of treatment in each of the target populations is approximately 12 months, for the purposes of the analysis it was pragmatically assumed that annual incidence \approx prevalence, thus removing the need for cascading of patients through the forward estimates period. This is not appropriate given that the mean duration of

treatment in MONARCH-2 in the follow-up study was 18.9 cycles or approximately 17 months (Sledge 2019).

- 6.60 The submission assumed that abemaciclib and ribociclib would have a 50% share of the market each. It is unclear whether the market will be shared evenly. There will be some patients who are unable to have ribociclib and will choose abemaciclib due to a history of cardiac issues or switch due to QT prolongation. Ribociclib has also been approved longer and is more established in the clinical community.

Quality Use of Medicines

- 6.61 The submission did not propose any activities to support the quality use of medicines. Given that there are varying adverse effect profiles across the different CDK1's further education should be provided to highlight the adverse effects more commonly associated with abemaciclib such as diarrhoea.

Financial Management –Risk Sharing Arrangements

- 6.62 The submission did not propose a risk sharing arrangement.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of abemaciclib in combination with fulvestrant, for the treatment of non-premenopausal patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) inoperable locally advanced or metastatic breast cancer, on a cost-minimisation basis with ribociclib in combination with fulvestrant.
- 7.2 The PBAC welcomed the input from individuals, Breast Cancer Network Australia and Medical Oncology Group of Australia and noted that the use of abemaciclib may provide more treatment options for patients diagnosed with metastatic disease.
- 7.3 The PBAC noted that the proposed restriction for abemaciclib only included patients who have prior endocrine resistance and thus excluded de novo patients. While the ITT population in MONARCH-2 did not include patients with de novo metastatic disease, based on the post hoc exploratory analysis of the 44 patients with de novo metastatic disease who were enrolled prior to the protocol amendment, the data indicated that the 28 patients who received abemaciclib plus fulvestrant appeared to derive a similar benefit to the ITT population. The PBAC also noted that use of CDK1+fulvestrant is likely to be minimal in de novo patients as these patients would likely prefer an oral NSAID than intramuscular injections of fulvestrant. Therefore, the PBAC considered that a listing, including de novo metastatic patients, would be appropriate for abemaciclib and consistent with both the TGA registered indication for abemaciclib and the listing recommended for ribociclib at the November 2020 PBAC meeting.

- 7.4 The PBAC considered the existing listing for abemaciclib in combination with NSAIs (initial and continuing) should be amended to include the combination use with fulvestrant; and a new grandfather listing be added.
- 7.5 The PBAC considered the indirect comparison presented in the submission supported the claim of non-inferiority of efficacy for abemaciclib compared with ribociclib. However, the PBAC noted that the indirect comparison did not allow for a meaningful quantitative comparison of the harms of abemaciclib and ribociclib due to the differing side effect profiles and the impact of the higher initial abemaciclib starting dose on dose reductions and discontinuations.
- 7.6 The submission acknowledged that abemaciclib is associated with higher rates of diarrhoea than ribociclib, but did not include any additional costs for the treatment of diarrhoea in the cost-minimisation analysis, stating that the cost impact would be minimal. The PBAC recalled that at its March 2019 consideration of abemaciclib (for use in combination with an NSAI), it considered that abemaciclib is associated with a higher incidence of diarrhoea compared with ribociclib. The PBAC maintained this view whilst noting the additional evidence presented in the current submission.
- 7.7 The PBAC accepted the following equi-effective doses:
- abemaciclib 260.7 mg/day (based on a mean relative dose intensity (RDI) of 86.9%) for 28 days every 28-day cycle is equivalent to
 - ribociclib 511.2 mg/day (based on a mean RDI 85.2%) for 21 days every 28-days.
- 7.8 The PBAC noted the revised cost-minimisation analysis presented in the PSCR which removed the ECG costs. The PBAC considered this appropriate and consistent with its March 2019 recommendation for abemaciclib (para 7.9 Abemaciclib PSD, March 2019 PBAC meeting).
- 7.9 The PBAC recalled that it had recommended ribociclib + fulvestrant in November 2020 based on a weighted price derived from a:
- cost minimisation analysis, based on ribociclib + fulvestrant compared with ribociclib + NSAI as first line treatment in the metastatic setting (i.e. including patients with de novo metastatic disease and those who received endocrine therapy in the (neo)adjuvant setting); and a
 - cost-effectiveness analysis, based on ribociclib + fulvestrant versus everolimus + exemestane in second/subsequent line treatment.

Overall, in its November 2020 consideration of ribociclib + fulvestrant “the PBAC considered the prices proposed in each of the settings were reasonable, and the resubmission’s overall proposal of a price that is the same as the current price for use in combination with NSAIs was appropriate”. (para 5.9, ribociclib PSD, November 2020 PBAC meeting)

- 7.10 Consistent with its recommendation at the November 2020 meeting, the PBAC considered that the price of abemaciclib, when used in combination with fulvestrant, should be no higher than the price for the existing listing of abemaciclib when used in combination with an NSAID.
- 7.11 The PBAC considered the submission overestimated the uptake rates across the populations and that the assumption of full treatment compliance is unlikely to be realised in practice. However, the PBAC considered the financial risk could be mitigated by including this expanded listing within the same Risk Sharing Arrangement as advised in its recommendation for ribociclib in combination with fulvestrant, with no increase to the agreed caps for ribociclib to ensure there is no net financial cost to the government.
- 7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because abemaciclib in combination with fulvestrant is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ribociclib in combination with fulvestrant, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Amend existing listings to permit use in combination with fulvestrant, in certain circumstances, as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ABEMACICLIB					
abemaciclib 150 mg tablet, 56	11868P	1	56	5	Verzenio
abemaciclib 100 mg tablet, 56	11871T	1	56	5	Verzenio
abemaciclib 50 mg tablet, 56	11876C	1	56	5	Verzenio
		Max.Qty multiplier = 1; Repeat increases: nil			
Edit existing Restriction Summary 10039 / ToC: 10032 to appear as follows:					
Concept ID	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia					
Prescribing Rule Level	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				

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	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors for the purposes of this restriction are abemaciclib, palbociclib and ribociclib
	Indication: Locally advanced or metastatic breast cancer
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must be untreated with each of: (i) abemaciclib, (ii) palbociclib, (iii) ribociclib; or
	Patient must have developed an intolerance to at least one of the above drugs (other than this drug) of a severity necessitating permanent treatment withdrawal
	AND
	Clinical criteria:
	The condition must be hormone receptor positive
	AND
	Clinical criteria:
	The condition must be human epidermal growth factor receptor 2 (HER2) negative
	AND
	Clinical criteria:
	The condition must be inoperable
	AND
	Clinical criteria:
	Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less
	AND
	Clinical criteria:
	The treatment must be in combination, where the patient has never been treated with endocrine therapy for advanced/metastatic disease, with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant; or
	The treatment must be in combination, where the patient has recurrence/progressive disease despite being treated with endocrine therapy for advanced/metastatic disease, with fulvestrant only
	AND
	Clinical criteria:
	The treatment must not be in combination with another drug of the same pharmacological class as this drug
	Population criteria:
	Patient must not be premenopausal
Edit Restriction Summary 10050 / ToC: 10019 to appear as follows:	
	Indication: Locally advanced or metastatic breast cancer
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant
	AND
	Clinical criteria:
	The treatment must not be in combination with another drug of the same pharmacological class as this drug
	AND
	Population criteria:
	Patient must not be premenopausal

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Add Restriction Summary: NEW / ToC: NEW	
Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia
	Indication: Locally advanced or metastatic breast cancer
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - 'Grandfather' arrangements
	Clinical criteria:
	Patient must have received treatment with this drug for this PBS-indication prior to [insert date of PBS listing]
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition
	AND
	Clinical criteria:
	Patient must have been untreated with each of: (i) abemaciclib, (ii) palbociclib, (iii) ribociclib, at the time non-PBS supply was initiated; or
	Patient must have developed an intolerance to at least one of the above drugs (other than this drug) of a severity necessitating permanent treatment withdrawal
	AND
	Clinical criteria:
	The condition must be hormone receptor positive
	AND
	Clinical criteria:
	The condition must be human epidermal growth factor receptor 2 (HER2) negative
	AND
	Clinical criteria:
	The condition must be inoperable
	AND
	Clinical criteria:
	Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 2 at the time of non-PBS supply was initiated
	AND
	Clinical criteria:
	The treatment must be in combination with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant, where the patient had never been treated with endocrine therapy for advanced/metastatic disease at the time non-PBS supply was initiated; or
	The treatment must be in combination with fulvestrant only, where at the time non-PBS supply was initiated, the patient had recurrent/progressive disease despite being treated with endocrine therapy for advanced/metastatic disease
	AND
	Clinical criteria:
	The treatment must not be in combination with another drug of the same pharmacological class as this drug
	AND
	Population criteria:
	Patient must not be premenopausal
	Administrative Advice: Patients 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.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.