

6.06 RIBOCICLIB, 200 mg Tablets, Kisqali[®], Novartis Pharmaceuticals Australia Pty Limited

1 Purpose of submission

- 1.1 The submission requested an extension to the current Authority Required listing for ribociclib to include first and second–line combination use with fulvestrant.
- 1.2 The submission was based on a cost-minimisation analysis of ribociclib plus fulvestrant (RIBO+FULV) versus ribociclib plus non-steroidal aromatase inhibitors (RIBO+NSAI) for the first-line treatment of patients who have not been previously treated with an aromatase inhibitor for advanced breast cancer. A cost-effectiveness analysis versus everolimus plus exemestane (EVE+EXE) was presented for the second-line treatment of patients who have progressed on first-line aromatase inhibitor monotherapy.

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

Component	Description
Population	Non-premenopausal patients with HR+/HER2– locally advanced or metastatic breast cancer.
Intervention	RIBO (600 mg po on days 1-21 of a 28-day cycle) + FULV (500 mg IM on day 1 and day 15 of a 28-day cycle, and day 1 every 28 days thereafter).
Comparators	First-line (endocrine-sensitive and endocrine-resistant) setting – RIBO (600 mg po on days 1-21 of a 28-day cycle) + NSAI (LET 2.5 mg po daily or ANA 1 mg po daily). Second-line setting – EVE (10 mg po daily) + EXE (25 mg po daily).
Outcomes	Progression free survival (PFS) Overall survival (OS) Overall Response Rate (ORR) Health related quality of life (HRQoL) Adverse events (AE)
Clinical claim	RIBO+FULV provides non-inferior effectiveness and safety compared to RIBO+NSAI in the first-line treatment setting. RIBO+FULV provides superior effectiveness and safety to EVE+EXE in the second-line treatment setting.

EVE= everolimus; EXE= exemestane; FULV= fulvestrant; HR+= hormone receptor positive; HER2- = human epidermal growth factor receptor 2-negative; IM= intramuscular; NSAI= non-steroidal aromatase inhibitor; po= per oral; mg=milligram; RIBO= ribociclib; ANA= anastrozole; LET= letrozole.

Source: Table 1-1, p40 of the submission and added during the evaluation.

2 Background

- 2.1 Ribociclib is currently PBS listed for use in combination with a non-steroidal aromatase inhibitor (NSAI; letrozole or anastrozole) as first-line therapy for hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer.
- 2.2 Ribociclib in combination with fulvestrant had not been considered by the PBAC previously.

- 2.3 Fulvestrant (as combination therapy or as monotherapy) is not currently PBS listed for any indication. A separate submission (sponsored by AstraZeneca) requesting listing of fulvestrant for the treatment of patients with HR+, HER2- advanced breast cancer was also considered at the July 2020 PBAC meeting.

Registration status

- 2.4 Ribociclib was first approved by the Therapeutic Goods Administration (TGA) in October 2017 and later updated in February 2020 for the following indication:

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

The TGA indication further notes that “In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist”.

- 2.5 Fulvestrant monotherapy under the brand name, Faslodex (AstraZeneca), 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.
- 2.6 The sponsor of this submission (Novartis/Sandoz) lodged a TGA submission seeking registration of a generic form of fulvestrant in September 2019. The TGA approved registration of the generic form in May 2020 with the indication: “... for the treatment of postmenopausal women with hormone-receptor positive, locally advanced or metastatic breast cancer who have progressive disease following prior tamoxifen therapy” (i.e. the same indication as non-generic fulvestrant).
- 2.7 The TGA indication for ribociclib includes combination use with fulvestrant. Consequently, combination use (in first or second-line) is considered to be “on-label”.

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

3 Requested listing

- 3.1 The requested listing is outlined below. The submission proposed amending the existing listings for ribociclib (initial and continuing) to allow use in combination with fulvestrant (changes to the existing first-line listings are shown in italics) and adding new grandfather listings and new second-line treatment listings for ribociclib.

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Essential elements of the requested listing for ribociclib

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RIBOCICLIB, 200 MG TABLETS	1	63 ^a	5	PP: \$5512.13 ^b	Kisqali, Novartis Pharmaceuticals Australia Pty Limited
		42 ^a		EP-1L: \$ [REDACTED]	
		21 ^a		EP-2L: \$ [REDACTED]	

Category/Program:	GENERAL – General Schedule
PBS indication:	Locally advanced or metastatic breast cancer
Treatment phase:	Initial treatment- FIRST LINE
Restriction:	<input checked="" type="checkbox"/> Authority Required – telephone/electronic
Clinical criteria:	Patient must not have previously been treated with <i>endocrine therapy</i> for advanced or metastatic breast cancer, AND Patient must not have previously been treated with abemaciclib OR palbociclib OR patient must have developed an intolerance to abemaciclib 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 or <i>fulvestrant</i> AND The treatment must not be in combination with abemaciclib or palbociclib
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
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised Special Pricing Arrangements apply
Cautions:	QT interval monitoring is required for patients treated with this drug
Treatment Phase:	Continuing- FIRST LINE
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not have developed 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 or <i>fulvestrant</i> , AND The treatment must not be in combination with abemaciclib or palbociclib
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
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised Special Pricing Arrangements apply
Cautions:	QT interval monitoring is required for patients treated with this drug

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Treatment Phase:	Initial treatment – Grandfather patients – FIRST LINE
Clinical criteria:	<p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [insert date of PBS listing], AND</p> <p>Patient must not have previously been treated with endocrine therapy for advanced or metastatic breast cancer prior to initiating treatment with this drug for this condition, AND</p> <p>Patient must not have previously been treated with abemaciclib or palbociclib OR patient must have developed an intolerance to abemaciclib or palbociclib of a severity necessitating permanent treatment withdrawal, AND</p> <p>The condition must be hormone receptor positive, AND</p> <p>The condition must be human epidermal growth factor receptor 2 (HER2) negative, AND</p> <p>The condition must be inoperable, AND</p> <p>Patient must have had 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</p> <p>Patient must not have developed disease progression while receiving treatment with this drug for this condition, AND</p> <p>Patient must have stable or responding disease, AND</p> <p>The treatment must be in combination with anastrozole or letrozole or fulvestrant AND</p> <p>The treatment must not be in combination with abemaciclib or palbociclib</p>
Population criteria:	Patient must not be premenopausal.
Administrative advice:	<p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p> <p>For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p> <p>This Grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria</p>
Cautions:	QT interval monitoring is required for patients treated with this drug
Treatment Phase:	Initial treatment – Second line and subsequent line
Clinical criteria:	<p>Patient must have developed progressive disease following treatment with endocrine therapy for advanced or metastatic breast cancer, AND</p> <p>The condition must be hormone receptor positive, AND</p> <p>The condition must be human epidermal growth factor receptor 2 (HER2) negative, AND</p> <p>The condition must be inoperable, AND</p> <p>Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, AND</p> <p>The treatment must be in combination with fulvestrant, AND</p> <p>Patients must not have previously received treatment with a CDK inhibitor in the first-line setting, AND</p> <p>The treatment must not be in combination with abemaciclib or palbociclib</p>
Population criteria:	Patient must not be premenopausal.
Treatment Phase:	Continuing treatment – Second line and subsequent line
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND</p> <p>Patient must not have developed disease progression while receiving treatment with this drug for this condition, AND</p> <p>Patient must have stable or responding disease, AND</p> <p>The treatment must be in combination with fulvestrant AND</p> <p>The treatment must not be in combination with abemaciclib or palbociclib</p>
Population criteria:	Patient must not be premenopausal.
Cautions:	QT interval monitoring is required for patients treated with this drug
Treatment Phase:	Initial treatment – Grandfather patients – Second line and subsequent line
Clinical criteria:	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [insert date of PBS listing], AND

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	<p>Patient must have developed progressive disease following treatment with endocrine therapy for advanced or metastatic breast cancer prior to initiating treatment with this drug for this condition, AND</p> <p>Patients must not have previously received treatment with a CDK inhibitor in the first-line setting, AND</p> <p>The condition must be hormone receptor positive, AND</p> <p>The condition must be human epidermal growth factor receptor 2 (HER2) negative, AND</p> <p>The condition must be inoperable, AND</p> <p>Patient must have had 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</p> <p>Patient must not have developed disease progression while receiving treatment with this drug for this condition, AND</p> <p>Patient must have stable or responding disease, AND</p> <p>The treatment must in combination with fulvestrant, AND</p> <p>The treatment must not be in combination with abemaciclib or palbociclib</p>
Population criteria:	Patient must not be premenopausal.
Administrative advice:	<p>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.</p> <p>This Grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria</p>
Cautions:	QT interval monitoring is required for patients treated with this drug

PP= published price; EP-1L= proposed effective price first-line; EP-2L= proposed effective price second-line.

^a 63 tablets per cycle (600mg/day) = 3 x 21 days; 42 tablets/cycle (400mg/day) = 2 x 21 days; 21 tablets/cycle (200mg/day) = 1 x 21 days.

^b Published price. Special pricing arrangements apply for the effective prices. Approved ex-manufacturer price for ribociclib 600mg is \$ [REDACTED]. The submission proposed indication-specific prices for first- and second-line treatment. In first-line, these are \$ [REDACTED], \$ [REDACTED], and \$ [REDACTED] for 63, 42, and 21 tablets, respectively. In second-line, these are \$ [REDACTED], \$ [REDACTED], and \$ [REDACTED], respectively.

Source: Compiled during the evaluation based on Tables 1-16 to 1-19, pp61-64 of the submission.

- 3.2 The effective DPMQ of ribociclib for its current listing is \$ [REDACTED] (600 mg, 63 tablets pack). The requested effective DPMQs for the proposed new listings (based on 600 mg, 63 tablets pack) are: \$ [REDACTED] for first-line treatment ([REDACTED] % [REDACTED] than the current listing); and \$ [REDACTED] for second-line treatment ([REDACTED] the price of the current listing).
- 3.3 The proposed DPMQ of the fulvestrant component is \$ [REDACTED] (AEMP of \$ [REDACTED]) 500 mg IM injection. The submission stated that the sponsor of generic fulvestrant, Sandoz Australia, has committed to supplying at this price. The submission also proposed a listing for fulvestrant specific to use in combination with ribociclib (requested restriction not included herein). The PBAC considered that the listing for fulvestrant (for use in combination with ribociclib) should be a line-agnostic listing combining initial and continuing treatment.
- 3.4 In the Pre-Sub-Committee Response (PSCR) the sponsor proposed the following amendments to the proposed restriction (deletions in strikethrough, additions underlined):
- 1L: “Patient must not have previously been treated with ~~aromatase inhibitor~~ endocrine therapy for advanced or metastatic breast cancer...”.

- 2L: “Patient must have developed progressive disease following treatment with ~~aromatase inhibitor~~ endocrine therapy for advanced or metastatic breast cancer...”.

If fulvestrant monotherapy was to become available on the PBS (see agenda item 5.06 of this meeting), the PBAC considered the intent of this amendment was reasonable because in the first-line setting it would restrict use of RIBO+FULV to the first CDKI+endocrine therapy (NSAI/fulvestrant) for locally advanced/metastatic disease (except in the circumstance where the patient has had severe intolerance to other CDKIs). The PBAC noted that, consistent with the existing restrictions for CDKIs+NSAIs, the proposed criterion excluding prior endocrine therapy in the ‘first-line’ setting would still permit patients with visceral disease who are treated with chemotherapy before endocrine therapy to access RIBO+FULV. As such, ‘first-line endocrine therapy-containing treatment’ may be a more accurate treatment phase description. A consolidated restriction covering first and subsequent line use would also resolve this.

- 3.5 Inclusion of grandfather patients who have previously received non-subsidised treatment with RIBO+FULV in the first- and second-line settings was also requested.

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

4 Population and disease

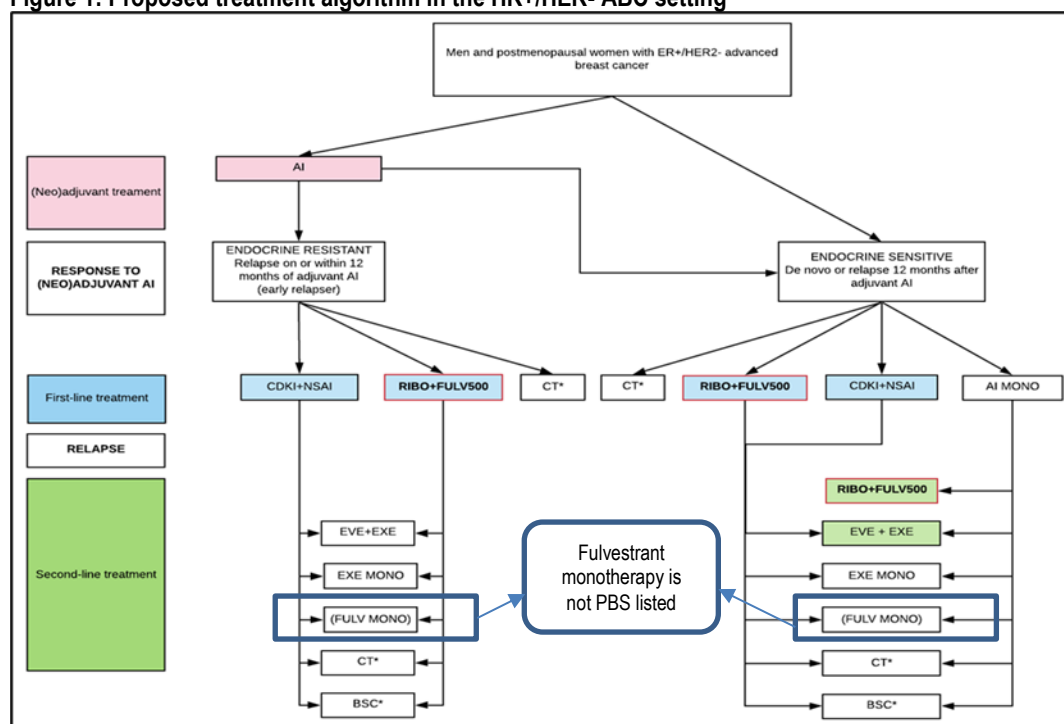
- 4.1 Breast cancer is the most common cancer in women and the second most common cancer globally.¹ The subtype addressed in this submission, Luminal A (HR+/HER2-, low Ki67 expression), is the predominant form of advanced breast cancer. Luminal A cancers are low-grade, tend to grow slowly and have the best prognosis due to their responsiveness to hormonal/endocrine therapy. However, endocrine therapy resistance leading to disease progression eventually occurs in many patients, representing a significant issue for optimal clinical management.
- 4.2 The target population in the submission was non-premenopausal patients with HR+/HER2- locally advanced (stage III locally advanced disease that is not amenable to potentially curative surgical resection) or metastatic (stage IV) breast cancer.
- 4.3 The PBAC had previously amended the PBS restrictions for five endocrine therapies for breast cancer to allow males to access subsidised treatment when the criteria ‘The patient must be postmenopausal’ was replaced with ‘Patient must not be premenopausal’ (para. 3.1, Five endocrine therapies, Public Summary Document (PSD), November 2014 PBAC meeting).²

¹ Bray, F., et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*. 2018 Nov;68(6):394-424.

² PBAC (November 2014) Public Summary Document: Anastrozole, Everolimus, Exemestane, Goserelin and Letrozole.

- 4.4 The submission stated that oestrogen deprivation, using hormonal therapy, is the standard first line treatment for patients with HR+/HER2- advanced breast cancer, except those with immediately life-threatening disease (Cardoso et al. 2016). Specific hormonal therapies used in this treatment setting include aromatase inhibitors, selective oestrogen receptor modulators (tamoxifen) and oestrogen receptor antagonists (fulvestrant).
- 4.5 Aromatase inhibitors (AIs) inhibit the aromatase enzyme and prevent oestrogen synthesis. There are two general categories of AIs: (1) the nonsteroidal inhibitors (NSAIs), letrozole and anastrozole, which bind competitively with aromatase, and (2) the steroidal inhibitor, exemestane, which irreversibly inactivates aromatase. For combination therapy with CDK4/6 inhibitors (CDKIs) such as ribociclib, NSAIs are generally preferred over exemestane, and the current PBS restriction allows ribociclib in combination with NSAIs only.
- 4.6 The proposed clinical treatment algorithm is shown in Figure 1.

Figure 1: Proposed treatment algorithm in the HR+/HER- ABC setting



ABC= advanced breast cancer; AI= aromatase inhibitor; BSC= best supportive care; CDKI= cyclin-dependent kinase inhibitor; CT= chemotherapy; ER+= oestrogen receptor-positive; EVE= everolimus; EXE= exemestane; HER2-= human epidermal growth factor receptor 2-negative; MONO= monotherapy; NSAI= non-steroidal aromatase inhibitor; FULV500/FULV= fulvestrant 500mg. * The submission stated that chemotherapy is generally reserved for patients with visceral crisis or who are not considered suitable candidates for the highlighted treatments.

Note: The clinical management algorithm proposed by this submission includes treatment with RIBO+FULV500 in the first- and second-line advanced breast cancer treatment settings (shown in red, bold outline).

Source: Figure 1-2, p51 of the submission, with additional blue coloured boxes overlaid during the evaluation.

- 4.7 Fulvestrant monotherapy was included as a second-line treatment option in both the current and proposed treatment algorithms. However, it is not PBS listed for any

indication. As noted earlier, a separate submission requesting listing of fulvestrant was considered at the July 2020 PBAC meeting.

- 4.8 The ESC considered that most patients with HR+ HER2- advanced or metastatic breast cancer would currently receive first-line treatment with CDKI+NSAI. The submission proposes RIBO+FULV as an alternative to CDKI+NSAI in this group of patients. This first-line group includes patients who: present with de-novo advanced/metastatic disease (treatment naïve), develop advanced/metastatic disease more than 12 months after completing adjuvant treatment with an NSAI for early breast cancer (endocrine sensitive) and those who relapsed within 12 months of prior (neo)adjuvant excluding those treated with NSAI.
- 4.9 RIBO+FULV might also be an option for patients who develop advanced/metastatic disease less than 12 months after completing (or while on) adjuvant treatment with an AI for early breast cancer (NSAI-resistant). These patients are typically excluded from first-line Phase 3 studies (e.g., they were excluded from MONALEESA-2). Similarly in MONALEESA-3, women who are NSAI-resistant were included in the second-line subgroup. These women, who would be considered second-line in clinical trials would be included in the proposed first-line restriction, which is for patients with no prior endocrine therapies in the advanced or metastatic setting.
- 4.10 In the second line setting, RIBO+FULV would be an option for patients who received single-agent NSAI first-line before the CDKIs were available. This prevalent group of patients is likely to decrease over time as the incidence of patients starting treatment in the advanced/metastatic setting on single-agent NSAI decreases. In addition, single-agent NSAIs may be used first-line in patients with low burden disease or for patients with an indolent disease course.⁴
- 4.11 The ESC also noted that describing lines of treatment in the submission as first-line and second-line does not adequately capture the expected clinical use. Patients who receive “second-line” treatment may have had prior hormonal therapies and chemotherapies. As such, describing the lines of treatment as first-line (treatment naïve in the metastatic setting) and subsequent-line may be a more accurate description of clinical use of RIBO+FULV. “First-line”, for PBS purposes, would include patients who develop advanced/metastatic disease after completing adjuvant treatment for early breast cancer (endocrine sensitive or first-line endocrine resistant), consistent with the wording in the restriction around not receiving prior treatment for advanced or metastatic breast cancer. In the second-line setting, the data available to support use of RIBO+FULV were limited to the second-line setting and did not include later lines, however the PBS restriction would allow use in subsequent lines.
- 4.12 The ESC noted that clinicians generally try to continue endocrine therapies (alone or in combination with CDKI) as long as possible because they are less toxic than combined use with targeted therapies (eg. everolimus) and less toxic than

chemotherapy. Toxicities of therapies can vary between patients, for example many patients will tolerate capecitabine better than EVE+EXE.

- 4.13 Ribociclib is a small molecule inhibitor of CDK4/6 that can be used in combination with AI to treat patients with HR+ locally advanced or metastatic breast cancer. By targeting CDK4 and CDK6, ribociclib interferes with the cell cycle progression and cell proliferation pathways to slow down the growth of cancer cells. Fulvestrant works by down-regulating and degrading the oestrogen receptor. It binds to the oestrogen receptors, making them change shape so that cancer cells are unable to bind to oestrogen, thereby preventing the growth stimulatory effects of oestrogen.

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

5 Comparator

- 5.1 The submission nominated RIBO+NSAI as the main comparator for the first-line, and EVE+EXE for the second-line treatment of HR+/HER2- locally advanced or metastatic breast cancer. Although the international clinical guidelines differ on the preferred sequence of first-line and subsequent-line therapies, the commentary considered the choice of the comparators seems reasonable given that:

- First-line: RIBO+NSAI is PBS listed for the first-line treatment of HR+/HER2- locally advanced or metastatic breast cancer patients who have not received prior aromatase inhibitor therapy for advanced or metastatic breast cancer, and may be preferred for patients who are more likely to benefit from and can tolerate the combination therapy compared to aromatase inhibitor monotherapy. Chemotherapy is generally reserved for patients with life-threatening visceral crisis, and exemestane monotherapy is often used in the second-line setting. Given that RIBO+FULV will be offered as one of the alternatives to RIBO+NSAI in the first-line, the choice of the comparator seems appropriate. The ESC agreed with the commentary that the nominated comparator in the first-line setting was appropriate.
- Second-line / subsequent-line: For metastatic (Stage IV) patients who have progressed on first-line endocrine-therapy, EXE+EVE is PBS listed and is often the preferred treatment option. Although exemestane monotherapy, chemotherapy and best supportive care are other feasible options, they are generally reserved for patients for whom the alternative treatments are not considered suitable. Therefore, the commentary considered EXE+EVE was a suitable comparator choice. The ESC noted that use of EXE+EVE appears to be decreasing, based on PBS utilisation data. The ESC considered that a mix of other treatments such as chemotherapy (e.g. capecitabine) and endocrine therapies (e.g. tamoxifen) could also be considered comparators for some patients.

- 5.2 The submission also nominated palbociclib plus fulvestrant as a near market comparator as it is of the same therapeutic class with a similar TGA indication. This

approach was reasonable, however, palbociclib plus fulvestrant was not considered in either the effectiveness or cost-effectiveness analyses. Abemaciclib plus fulvestrant is also a potential near market comparator that was not considered.

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 6 individuals via the Consumer Comments facility on the PBS website. The comments from patients currently accessing ribociclib described the benefits of treatment in combination with NSAIs. There were also comments from patients who were treated with aromatase inhibitors prior to PBS listing of ribociclib, or who have received other treatments for metastatic breast cancer, meaning they are unable to access ribociclib under the current restrictions. These patients commented that ribociclib may be of benefit to them but was not accessible due to the high cost of treatment.
- 6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) and the MOGA breast cancer expert group in support of PBS listing of RIBO+FULV. Both groups commented that listing of this combination is especially important for 1) second-line treatment for patients who were on an aromatase inhibitors alone as first line treatment before CDK4/6 inhibitors were PBAC listed; and 2) first-line treatment for patients who relapse with metastatic disease during or shortly after completing treatment with an aromatase inhibitor for early stage breast cancer. Both groups also noted that ribociclib in combination with fulvestrant is effective at prolonging both progression free survival and overall survival, is well-tolerated, and enables quality of life to be maintained for longer by delaying the need for chemotherapy.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for RIBO+FULV, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the MONALEESA-3 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for ribociclib + fulvestrant, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)³, based on a comparison with placebo + fulvestrant.

³ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Clinical trials

6.5 The submission was based on three main trials, which were the basis of the unanchored matched adjusted indirect comparisons (MAIC) presented:

- MONALEESA-3 was a randomised, double-blind study of RIBO+FULV versus placebo+FULV (PBO+FULV) for the treatment of men and postmenopausal women with HR+/HER2- ABC who have received no or only one line of prior endocrine treatment. Although male patients were eligible for enrollment after a protocol amendment, no male patients were enrolled. Out of the 484 patients in the RIBO+FULV arm, 237 patients were either treatment naïve⁴ or endocrine-sensitive⁵, 137 patients were resistant to endocrine therapy in the (neo)adjuvant setting⁶ and 100 patients had received one line of endocrine therapy in the advanced/metastatic setting.⁷ Data from MONALEESA-3 were used in both first-line and second-line treatment analyses.
- MONALEESA-2 was a randomised, double-blind, placebo-controlled study comparing RIBO+NSAI (n=334) with placebo+NSAI (PBO+NSAI, N=334) for the treatment of postmenopausal women with HR+/HER2- advanced breast cancer who had not received previous systemic therapy for advanced disease. Data from MONALEESA-2 were used only for the first-line analyses.
- BOLERO-2 was a randomised, double-blind, placebo-controlled study comparing EVE+EXE (N=485) with placebo+exemestane (PBO+EXE, N=239) in the treatment of postmenopausal women with oestrogen receptor-positive ABC who are refractory to NSAI (letrozole or anastrozole). BOLERO-2 enrolled patients who had failed prior hormonal therapy; 40% of enrolled patients had received only one prior line of therapy in the metastatic setting (40% had received two or more prior lines in the metastatic setting; the remaining 20% received prior hormonal therapy in the (neo)adjuvant setting). Data from BOLERO-2 were used only for the second-line analyses.

6.6 Details of the trials are provided in Table 2.

⁴ Newly diagnosed advanced/metastatic breast cancer, treatment naïve.

⁵ Disease relapse occurred more than 12 months from completion of (neo) adjuvant endocrine therapy (ET) with no treatment for ABC.

⁶ Disease relapse occurred on or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for ABC (i.e. endocrine-resistant). The subgroup used in the first-line MAIC, excluding those whose last (neo) adjuvant endocrine therapy was with anastrozole or letrozole. Thus, only 65 patients from this subgroup were included in the first-line MAIC.

⁷ Disease relapsed more than 12 months from completion of (neo)adjuvant ET and then subsequently progressed with documented evidence of progression after one line of ET (with either an anti-oestrogen or an AI) for ABC (second-line endocrine resistant) OR Advanced/metastatic breast cancer at diagnosis with documented evidence of progression after one line of ET (with either an anti-oestrogen or an AI).

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Main intervention/comparator studies		
MONALEESA-3	<p>MONALEESA-3: A randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.</p> <p>Slamon, DJ et al. 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, DJ et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer.</p>	<p>25 April 2018</p> <p>J Clin Oncol. 2018 Aug 20;36(24):2465-72.</p> <p>New England Journal of Medicine. 2020 Feb 6;382(6):514-24.</p>
MONALEESA-2	<p>A randomized double-blind, placebo-controlled study of LEE011 in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease.</p> <p>Hortobagyi et al. Ribociclib as First line Therapy for HR-Positive, Advanced Breast Cancer.</p> <p>Hortobagyi et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer.</p> <p>O'Shaughnessy 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>Verma 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>27 July 2016</p> <p>NEJM. 2016 Nov 3;375(18):1738-48.</p> <p>Annals of Oncology. 2018 Jul 1;29(7):1541-7.</p> <p>Breast cancer research and treatment. 2018 Feb 1;168(1):127-34.</p> <p>Breast cancer research and treatment. 2018 Aug 1;170(3):535-45.</p>
BOLERO 2	<p>A randomized double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole.</p> <p>Baselga et al. "Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer." New England Journal of Medicine 366(6): 520-529.</p> <p>Beck et al. Everolimus plus exemestane as first-line therapy in HR+, HER2- advanced breast cancer in BOLERO-2.</p> <p>Campone et al. Health-related quality of life and disease symptoms in postmenopausal women with hr+, her2- advanced breast cancer treated with everolimus plus exemestane versus exemestane monotherapy.</p> <p>Piccart et al. Everolimus plus exemestane for hormone receptor- positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Overall survival results from BOLERO-2.</p> <p>Yardley et al. (2013). Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression-free survival analysis.</p>	<p>Sep 2011</p> <p>NEJM. 2012 Feb 9;366(6):520-9.</p> <p>Breast cancer research and treatment. 2014 Feb 1;143(3):459-67.</p> <p>Current medical research and opinion. 2013 Nov 1;29(11):1463-73.</p> <p>Annals of oncology. 2014 Dec 1;25(12):2357-62.</p> <p>Advances in therapy. 2013 Oct 1;30(10):870-84.</p>

CSR= clinical study report; HER2-= human epidermal growth factor receptor-2 negative; HR+= hormone receptor-positive; mg= milligrams. Source: Table 2-3, pp73-75 of the submission.

6.7 For each treatment setting (first-line and second/subsequent-line) two types of indirect treatment comparisons were presented in the submission:

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- Effectiveness Analysis 2, an unanchored MAIC, which was used as the basis for the clinical claims (and was used in the economic model for the second-line setting); and
 - Effectiveness Analysis 1, a multiple-stepwise indirect treatment comparison, which was used as a supportive analysis.
- 6.8 The multiple-stepwise indirect treatment analyses presented required multiple linking studies and there were significant differences between the populations in these studies that would violate the assumptions required for such a comparison. There was heterogeneity across the trials in terms of HER2 status, the definition of HR positivity, World Health Organisation Eastern Cooperative Oncology Group (ECOG) performance status and prior treatments, and as such the ESC considered that Effectiveness Analysis 1 was less informative. The submission did not use Effectiveness Analysis 1 as the basis for the clinical claims or economic analyses and results of this analysis are not presented herein.
- 6.9 In the first-line treatment setting, the submission presented an unanchored MAIC between the RIBO+FULV arm of MONALEESA-3 (subgroup of patients with no prior treatment in the advanced/metastatic setting excluding those who were resistant to (neo)adjuvant NSAI) and the RIBO+NSAI arm of MONALEESA-2. For the second-line treatment setting, the submission presented an unanchored MAIC between a subgroup of the RIBO+FULV arm of MONALEESA-3 and a subgroup of the EVE+EXE arm of BOLERO-2 (both were subgroups of second-line patients).
- 6.10 The key features of the trials used in the MAICs are summarised in Table 3.

Table 3: Key features of the included evidence- MAICs

Trial	N	Design/ duration of follow-up (median)	Risk of bias	Patient population used in MAIC	Outcomes
RIBO+FULV vs RIBO+NSAI- FIRST LINE					
MONALEESA-3	ITT: RIBO+FULV: 484 PBO+FULV: 334	R, DB 39.4m (Jun 2019 cut-off, trial ongoing)	Low	Treatment-naïve for advanced breast cancer subgroup (includes de novo, relapsed >12 months from completion of prior (neo)adjuvant ET, or relapsed <12 months of prior (neo)adjuvant excluding those treated with NSAI (n = 302) ^a	PFS, OS
MONALEESA-2	RIBO+NSAI (LET): 334 PBO+FULV: 334	R, DB 26.3 m (Jun 2017 cut-off, trial ongoing)	Low	Treatment naïve (no prior therapy for advanced breast cancer)	PFS, OS
RIBO+FULV vs EVE+EXE- SECOND LINE					
MONALEESA-3	ITT: RIBO+FULV: 484 PBO+FULV: 334	R, DB 39.4 m	Low	Subgroup resistant to first-line AI monotherapy (n=100)	PFS, OS
BOLERO-2	ITT EVE+EXE: 485 PBO+EXE: 239	R, DB 39.3 m (Oct 2013 cut-off, trial completed)	Low	Subgroup resistant to first-line AI monotherapy (n=192, reduced to 101 after weighting)	PFS, OS

DB = double blind; ABC= advanced breast cancer; OS = overall survival; PFS = progression-free survival; R = randomised; OL=open label; AD= approved dose; LD, loading dose; RIBO= ribociclib; EXE= exemestane; AI= aromatase inhibitor; FULV= fulvestrant (full dose , 500mg); FULV250= fulvestrant 250mg; LET= letrozole; FULV500= fulvestrant 250mg; NSAI= non-steroidal aromatase inhibitor; LD, loading dose; NR, not reported; m= months; TTP= time to progression; ObRR= ;ANA= anastrozole; CBR= clinical benefit rate; ObRR= objective response rate.

^a Includes 237 patients who were first-line endocrine sensitive (de novo or patients who had relapsed ≥ 12 months after receiving endocrine therapy in the (neo)adjuvant setting) and 65 patients whose disease relapsed within 12 months of neoadjuvant therapy, excluding those with last (neo) adjuvant endocrine therapy with anastrozole or letrozole.

Source: Compiled during the evaluation based on Tables 2-14 to 2-18, pp88-95 of the submission; Table 2-60, 2-65, pp148, 157 of the submission.

6.11 The risk of bias in the three main trials included in the Effectiveness Analysis 2 is considered low. However, the risk of bias due to the indirect nature of the comparisons may be considered high. Unanchored MAICs can be more prone to uncertainty than anchored MAICs in that they do not use within-study randomised data, and are prone to confounding due to unaccounted for differences in prognostic factors across single arms of different studies.

Comparative effectiveness

6.12 PFS and OS outcomes from the key trials are shown in Table 4. Note the results are only presented for the whole trial population, whereas the data used in the unanchored MAICs were based on subgroups for MONALEESA-3 and BOLERO-2.

Table 4: Summary of survival outcomes in the key trials (whole trial population)

Outcomes	Proposed medicine n/N (%)	Comparator n/N (%)	HR (95% CI)
MONALEESA-3 (whole trial population)	RIBO+FULV500	PBO+FULV500	
Progression-free survival (Nov 2017 cut-off)			
Patients with event	210/484 (43.4%)	151/242 (62.4%)	0.593 (0.48, 0.73)
Median PFS months	20.5 m	12.8 m	
Overall survival (Nov 2017 cut-off, median follow-up 20.4 months)			
Patients with event	70/484 (14.5%)	50/242 (20.7%)	0.670 (0.46, 0.96)
Median OS months	NE	NE	
Overall survival (Jun 2019 cut-off, median follow-up 39.4 months)			
Patients with event	167/484 (34.5%)	108/242 (44.6%)	0.724 (0.57, 0.92)
Median OS months	NE	40.0 m	
MONALEESA-2 (whole trial population)	RIBO+NSAI (LET)	PBO+NSAI (LET)	
Progression-free survival			
Patients with event	140/334 (41.9%)	205 / 334 (61.4%)	0.568 (0.46, 0.70)
Median PFS months	25.3 m	16.0 m	
Overall survival			
Patients with event	50/334 (15.0%)	66/334 (19.8%)	0.75 (0.52, 1.08)
Median OS months	NE	33 m	
BOLERO-2 (whole trial population)	EVE+EXE	PBO+EXE	
Progression-free survival			
Patients with event	310/485 (63.9%)	200/239 (83.7%)	0.45 (0.38, 0.54)
Median PFS months	7.82 m	3.19 m	
Overall survival			
Patients with event	267/485 (55.1%)	143/239 (59.8%)	0.89 (0.73, 1.10)
Median OS months	31.0 m	26.6 m	

CI= confidence interval; FULV= fulvestrant; FULV500= fulvestrant 500mg; FULV250= fulvestrant 250mg; PBO= placebo; RIBO= ribociclib; ANA= anastrozole; LET= letrozole; HR= hazard ratio; m= months; NSAI= non-steroidal aromatase inhibitor; PFS= progression-free survival; NR= not reported; TTP= time to progression; DA= approved dose regimen; LD= loading dose regimen; EXE= exemestane; EVE=everolimus. Source: Compiled during the evaluation from Tables 2-26, 2-27, 2-29, 2-30, 2-32, 2-33; pp104-117 of the submission.

First-line setting

- 6.13 In the first-line setting, the primary analysis population was non-premenopausal patients with HR+/HER2- advanced breast cancer who had received no prior treatment in the advanced/metastatic setting and who are not refractory to (neo)adjuvant NSAI.
- 6.14 The submission presented an unanchored MAIC⁸ between the RIBO+FULV arm of MONALEESA-3 (only including the subgroups of patients who were (i) treatment naïve, (ii) endocrine sensitive, or (iii) resistant to endocrine therapy in the (neo)adjuvant

⁸ Note that the results presented in MAIC are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for MONALEESA-2 or MONALEESA-3. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

setting excluding those who were resistant to an NSAI⁹) and the RIBO+NSAI arm of MONALEESA-2 using inverse probability of treatment weighting (IPTW) methods, described by Austin and Stuart (2015).¹⁰ The submission stated that because patients in MONALEESA-2 represent a subset of patients in MONALEESA-3, patients in MONALEESA-3 were selected to match the inclusion criteria of the MONALEESA-2 trial. The covariates that were included are outlined in the table below (along with baseline characteristics before and after weighting) and were: age, race, ECOG status, grade, visceral disease, number of metastatic sites, and time since initial treatment.

- 6.15 The pre-PBAC response clarified that receipt of prior chemotherapy in the neo(adjuvant) setting was inadvertently left out of this analysis and provided updated results that included this factor as a covariate. This factor had only a small effect on the estimates, reducing the PFS HR from 0.92 (95% CI: 0.72, 1.18) to 0.89 (95% CI: 0.70, 1.14). Post-progression therapy was not adjusted for, which would not affect PFS, but could affect OS.

⁹ Only a subgroup of first-line endocrine-resistant patients were included in the MAIC – it excluded patients whose last endocrine therapy in the (neo)adjuvant setting was anastrozole or letrozole and who had a disease free interval < 12 months.

¹⁰ Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Statistics in medicine*. 2015 Dec 10;34(28):3661-79.

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Table 5: Covariates in the first-line unanchored MAIC: patient characteristics before and after weighting

Patient Characteristics – covariates that were matched for	MONALEESA-3 subgroup ^a		MONALEESA-2		MONALEESA-2 weighted	
	RIB+FUL		RIB+LET		RIB+LET	
	N=302		N=334		N=301.6	
Age category (years) - n (%)	n	%	n	%	n	%
18 to < 65	173	57.3	184	55.1	173	57.2
≥ 65	129	42.7	150	44.9	129	42.8
Race - n (%)						
White	250	82.8	269	80.5	248	82.3
Asian	33	10.9	28	8.4	34	11.2
Black or African American	2	0.7	10	3.0	4	1.2
Other	17	5.6	26	7.8	15	5.1
ECOG performance status –n (%)						
0	191	63.2	204	61.1	189	62.8
1	111	36.8	130	38.9	112	37.2
Missing	0	0.0	0	0.0	0	0.0
Histologic grade –n (%)						
Well differentiated	28	9.3	30	9.0	28	9.3
Moderately differentiated	161	53.3	143	42.8	160	53.1
Poorly differentiated	61	20.2	59	17.7	61	20.2
Undifferentiated	6	2.0	3	0.9	2	0.5
Unknown	46	15.2	99	29.6	51	16.8
Visceral disease –n (%)						
Yes	174	57.6	197	59.0	174	57.7
No	128	42.4	137	41.0	128	42.3
Number of metastatic sites involved-n (%)						
1	103	34.1	102	30.5	102	33.8
2	90	29.8	118	35.3	92	30.5
≥ 3	109	36.1	114	34.1	107	35.6
Time since initial diagnosis quartiles -n (%) *						
Q1	73	24.2	86	25.7	76	25.1
Q2	77	25.5	82	24.6	75	25.0
Q3	75	24.8	84	25.1	73	24.3
Q4	77	25.5	82	24.6	77	25.6

Source: Table 2. Demographic and clinical characteristics, p14 of 'C1 Analysis report', excluding variables that did not appear to be adjusted for in the main analysis based on the 'Parameters' tab of the spreadsheet titled 'Ribociclib March 2020 PBAC Submission_Attachment C1 Main Spreadsheet_FINAL_10Mar20.xlsm' (which were: stage and receipt of prior chemotherapy in the adjuvant setting).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FULV, fulvestrant; LET, letrozole; PBO, placebo; Q, quintile; RIBO, ribociclib; SD, standard deviation

^a Subgroup of patients who are treatment naïve and endocrine sensitive and a subset of the endocrine resistant subgroup

Note that the results presented in MAIC are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for MONALEESA-2 or MONALEESA-3. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.16 Kaplan-Meier plots showing weighted and unweighted PFS and OS for the first-line patients on RIBO+FULV in MONALEESA-3 and on RIBO+NSAI in MONALEESA-2 are shown in Figure 2.
- 6.17 The absolute difference in Kaplan-Meier estimated median PFS for RIBO+FULV (27.8 months) vs. RIBO+NSAI (letrozole) (25.3 months) was 2.5 (95%CI: -3.9, 10.9) months.

Table 6: Results of Cox proportional hazards regressions for PFS and OS for unanchored MAIC in the first-line setting

Endpoint	Weighted?	Arms		Cox Regression			P-value
				HR	95% CI		
		Active (N=302)	Comp (N=334*)		Lower	Upper	
RIBO+FULV vs RIBO+NSAI- FIRST LINE							
PFS	No	RIBO+FULV M3	RIBO+LET M2	0.924	0.726	1.177	0.522
PFS	Yes	RIBO+FULV M3	RIBO+LET M2	0.919	0.717	1.177	0.503
OS	No	RIBO+FULV M3	RIBO+LET M2	1.068	0.728	1.567	0.737
OS	Yes	RIBO+FULV M3	RIBO+LET M2	1.082	0.733	1.599	0.691

CI= confidence interval; FULV= fulvestrant; HR= hazard ratio; LET= letrozole; M2= MONALEESA-2; M3= MONALEESA-3; B2= BOLERO-2; OS= overall survival; PFS= progression-free survival; RIBO= ribociclib; EXE= exemestane; EVE= everolimus.

* First-line: The N's for the weighted subset of MONALEESA-2 (N=301.6) were less than the unweighted numbers (N=334).

Hazard ratios shaded in blue were assumed in the base case cost-minimisation and cost-effectiveness analyses.

Hazard ratios less than 1 favour RIBO+FULV over the comparators.

Source: Table 2-61, p153 of the submission.

Note that the results presented in MAIC are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for MONALEESA-2 or MONALEESA-3. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.20 The commentary noted that a higher proportion of patients took subsequent lines of treatment in the active arm of MONALEESA-3 (210/484, 43.4%) compared with the active arm of MONALEESA-2 (89/334, 26.6%). This could bias the OS hazard ratio in favour of RIBO+FULV compared to RIBO+NSAI, because it is likely that the subsequent treatments acted to extend survival.

6.21 Overall, given the baseline characteristics of the included subgroup of MONALEESA-3 and MONALEESA-2 were reasonably well balanced even before weighting, results from the MAIC analysis are similar to those obtained from a simple naïve comparison, in which the unadjusted PFS and OS for RIBO+FULV from MONALEESA-3 are compared directly to PFS and OS for RIBO+NSAI from MONALEESA-2. The ESC considered that the unanchored MAIC for the endpoint of PFS was likely to be valid for the claim of non-inferiority to RIBO+NSAI in the first-line setting, given the similar trial populations in MONALEESA-2 and MONALEESA-3. The ESC considered that the OS data from MONALEESA-2 and MONALEESA-3 were immature and the confidence intervals from the unanchored MAIC were wide (HR for OS: 1.08 (95% CI: 0.73, 1.6)).

Second-line setting

6.22 For the second-line treatment analysis, the subgroup of patients resistant to one line of prior endocrine therapy in the advanced/metastatic setting in the RIBO+FULV arm of MONALEESA-3 (n=100) was matched to the subgroup of second-line patients (excluding first-line patients and patients with two or more prior lines of treatment, n=192) in the EVE+EXE arm of BOLERO-2. Some of the covariates that were included are outlined in the table below (along with baseline characteristics before and after weighting).

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Table 7: Patient characteristics for second-line endocrine-resistant patients in MONALEESA-3 and BOLERO-2

Patient Characteristics	MONALEESA-3 subgroup ^a		BOLERO 2 subgroup ^b		BOLERO 2 weighted	
	RIB+FUL		EVE+EXE		EVE+EXE	
	N=100		N=192		101.4	
Age category (years) - n (%)	n	%	n	%	n	%
18 to < 65	41	41.0	103	53.6	37	36.8
≥ 65	59	59.0	89	46.4	64	63.2
Race - n (%)						
White	84	84.0	139	72.4	85	83.7
Asian	7	7.0	41	21.4	7	6.9
Black or African American	1	1.0	7	3.6	5	5.1
Other	8	8.0	5	2.6	4	4.3
ECOG performance status –n (%)						
0	71	71.0	121	63.0	71	69.6
1	29	29.0	68	35.4	29	29.0
Missing	0	0.0	3	1.6	1	1.4
Histologic grade –n (%)						
Well differentiated	9	9.0	24	12.5	10	9.5
Moderately differentiated	49	49.0	72	37.5	48	47.7
Poorly differentiated	18	18.0	30	15.6	20	19.4
Un-differentiated	1	1.0	65	33.9	23	22.8
Unknown	23	23.0	1	0.5	1	0.6
Visceral disease –n (%)						
Yes	70	70.0	113	58.9	72	71.1
No	30	30.0	79	41.1	29	28.9
Number of metastatic sites involved- n (%)						
1	17	17.0	55	28.6	17	16.9
2	36	36.0	56	29.2	36	35.3
≥ 3	47	47.0	81	42.2	48	47.8
Time since initial diagnosis quartiles - n (%) *						
Q1	31	31.0	42	21.9	34	33.2
Q2	15	15.0	58	30.2	14	14.2
Q3	24	24.0	49	25.5	23	22.5
Q4	30	30.0	43	22.4	30	30.1
Number of prior lines of ET in the advanced setting - n (%)						
0	0	0.0	0	0.0	0	0.0
1	100	100.0	192	100.0	101	100.0

Source: Table 4, p27 of C2 Analysis report excluding variables that did not appear to be adjusted for in the main analysis based on the 'Parameters' tab of the submission spreadsheet titled 'Ribociclib March 2020 PBAC Submission_Attachment C2 Main Spreadsheet_FINAL_10Mar20.xlsm' (which were: receipt of prior chemotherapy in the adjuvant setting).

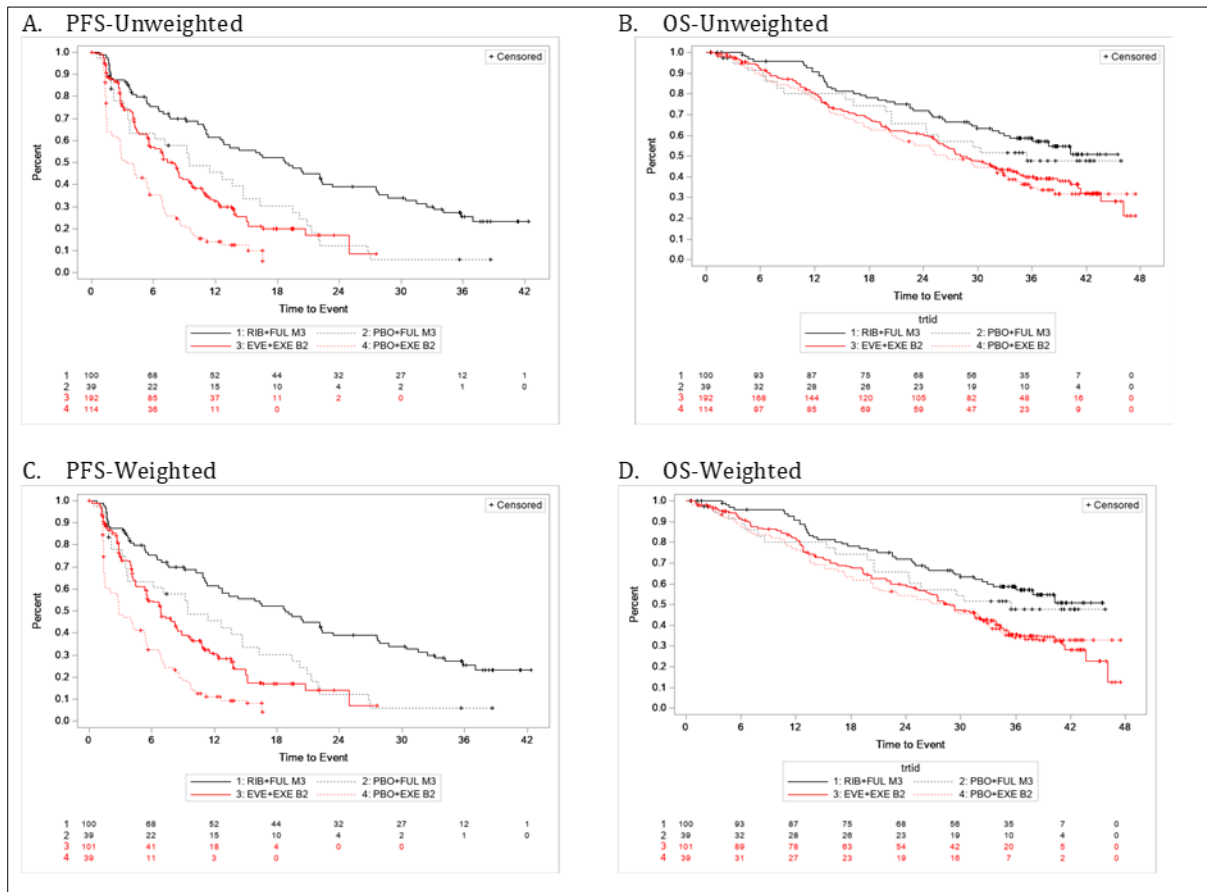
^a Subgroup who were resistant to one line of prior endocrine therapy in the advanced/metastatic setting

^b Subgroup of second-line patients (excluding first-line patients and patients with two or more prior lines of treatment)

Note that the results presented in MAIC are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for MONALEESA-2 or MONALEESA-3. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.23 Kaplan-Meier plots showing weighted and unweighted PFS and OS for the second-line patients on RIBO+FULV in MONALEESA-3 and on EVE+EXE in BOLERO-2 are shown in Figure 3.

Figure 3: Kaplan-Meier estimates of PFS and OS for second-line MAIC subgroups in MONALEESA-3 and BOLERO-2 (A) PFS Unweighted and (B) OS-Unweighted (C) PFS-Weighted (D) OS-Weighted



EVE= everolimus; EXE= exemestane; FULV= fulvestrant; OS= overall survival; PBO= placebo; PFS= progression-free survival; RIBO= ribociclib; M3= MONALEESA-3, B2= BOLERO-2.

Source: Figure 2-23, p161 of the submission.

Note that the results presented in MAIC are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for MONALEESA-2 or MONALEESA-3. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.24 The absolute difference in Kaplan-Meier estimated median PFS for RIBO+FULV second-line endocrine-resistant subpopulation (18.8 months) vs. EVE+EXE (7.8 months) was 11.0 (95% CI: 4.5, 16.0) months. After propensity score weighting, this difference increased slightly, by 1.1 months, to 12.1 months (95% CI: 5.9, 17.3).

6.25 The absolute difference in median OS in the RIBO+FULV second-line subpopulation is not available as the estimated median has not been reached. In BOLERO-2, before propensity score weighting, the estimated median OS was 28.2 (95% CI: 25.5, 34.3) months for EVE+EXE. After propensity score weighting, the estimated median OS was almost unchanged, at 28.2 (95% CI: 24.1, 33.9) months. Given the next analysis date for MONALEESA-3 is the second half of 2020, the updated analysis may provide a more precise estimate of the relative OS effectiveness of RIBO+FULV.

6.26 Results representing Cox proportional hazards regressions for both PFS and OS in the second-line setting in MONALEESA-3 vs BOLERO-2 are presented in Table 8. The hazard ratios shaded in blue in Table 8 formed the basis of the clinical claims and were applied in the base case analysis in the cost-utility model.

Table 8: Results of Cox proportional hazards regressions for PFS and OS for unanchored MAIC in the second-line setting

Endpoint	Weighted?	Arms		Cox Regression			
				HR	95% CI		P-value
		Active (N=100)	Comp (N= 192*)		Lower	Upper	
RIBO+FULV vs EVE+EXE – SECOND LINE							
PFS	No	RIBO+FULV M3	EVE+EXE B2	0.454	0.317	0.626	<0.0001
PFS	Yes	RIBO+FULV M3	EVE+EXE B2	0.397	0.270	0.558	<0.0001
OS	No	RIBO+FULV M3	EVE+EXE B2	0.600	0.421	0.828	0.005
OS	Yes	RIBO+FULV M3	EVE+EXE B2	0.561	0.379	0.797	0.004

CI= confidence interval; FULV= fulvestrant; HR= hazard ratio; LET= letrozole; M2= MONALEESA-2; M3= MONALEESA-3; B2= BOLERO-2; OS= overall survival; PFS= progression-free survival; RIBO= ribociclib; EXE= exemestane; EVE= everolimus.

* Second-line: The N's for the weighted subset of BOLERO-2 (N=102) were less than the unweighted numbers (N=192).

Hazard ratios shaded in blue were assumed in the base case cost-minimisation and cost-effectiveness analyses.

Hazard ratios less than 1 favour RIBO+FULV over the comparators.

Source: Table 2-61, p153 of the submission.

Note that the results presented in MAIC are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for MONALEESA-2 or MONALEESA-3. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.27 The ESC noted that patients in the whole trial population of BOLERO-2 were significantly more heavily pre-treated than those in MONALEESA-3. For example, 40% of patients in BOLERO 2 had received two or more prior lines in the metastatic setting, versus none in MONALEESA-3. The unanchored MAIC attempted to correct for this by including only patients from the subgroups who were being treated in the second-line setting. This substantially reduced the size of the population available for analysis:

- For MONALEESA-3, the whole trial population in the RIBO+FULV arm was 484 patients, while only 100 patients were included in the subgroup used in the second-line unanchored MAIC (i.e. excluding treatment-naive, endocrine-sensitive and patients who were resistant to one line of prior endocrine therapy in the advanced/metastatic setting).
- For BOLERO 2 the whole trial population in the EVE+EXE arm was 485 patients, while only 192 patients were included in the subgroup used in the second-line unanchored MAIC (i.e. excluding first-line patients and patients with two or more prior lines of treatment).

6.28 The PSCR stated that prior chemotherapy was not adjusted for in the MAIC analyses, however, for the trial data included in the MAIC (which was based on subgroups) the proportion of second-line patients with prior chemotherapy in the advanced setting was similar between trials (4% of patients in MONALEESA-3 and 5.2% of patients in BOLERO-2). The PSCR also stated the duration of follow-up was similar (39.4 months in MONALEESA-3 and 39.3 months in BOLERO-2).

- 6.29 The ESC noted that subsequent therapies in the active arms of MONALEESA-3 and BOLERO-2 appear to be similar (43.4% vs 40.2% overall, respectively) and thus the impact of subsequent therapies was unlikely to have a substantial impact on the OS.
- 6.30 Prior to weighting, patients in the MONALEESA-3 subgroup were older (59% were age \geq 65 years versus 46% in BOLERO 2), had fewer un-differential histological grade cancers (1% versus 34%), more patients with visceral disease (70% versus 59%), more metastatic sites involved (47% with \geq 3 metastatic sites involved versus 42%). The ESC considered that these represented substantial differences in baseline characteristics that were potential treatment effect modifiers. While weighting may have corrected for these factors, the ESC considered that the baseline imbalances indicated that patients included in the MONALEESA-3 trial were substantially different from the population included in BOLERO 2, increasing the likelihood of key differences in unobserved confounders. Overall, the ESC considered that it was not clear whether the unanchored MAIC presented for the second-line setting was unbiased. The pre-PBAC response noted that a number of additional variables (including region, bone-only lesions, progesterone receptor positive status and a range of prior-treatment related variables) were examined for both trials; and with the exception of region and race these variables did not have an impact on results, suggesting they are not potential confounders or treatment effect modifiers. The PBAC noted the limitations of the unanchored MAIC as outlined by the ESC, which increased the uncertainty in the results making it difficult to reliably assess the magnitude of benefit. However, the PBAC considered that it appeared that the subgroups included in the unanchored MAIC were adequately balanced for the comparison to be informative, notwithstanding its limitations.

Comparative harms

- 6.31 A summary of adverse events (AEs) in the three main trials is provided in Table 9.

Table 9: Summary of key adverse events in the three main trials

Trial ID	Intervention		Comparator	
	RIBO+FULV500 (N=483)		PBO+FULV500 (N=241)	
MONALEESA-3	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
All deaths	70 (14.5)	-	50 (20.7)	-
On-treatment deaths	13 (2.7)		8 (3.3)	
AEs	479 (99.2)	378 (78.3)	231 (95.9)	71 (29.5)
Suspected drug-related	461 (95.4)	326 (67.5)	164 (68.0)	19 (7.9)
Serious AEs	138 (28.6)	114 (23.6)	40 (16.6)	34 (14.1)
Suspected drug-related	54 (11.2)	44 (9.1)	6 (2.5)	4 (1.6)
AEs of special interest	444 (91.9)	326 (67.5)	156 (64.7)	32 (13.3)
Suspected drug-related	396 (82.0)	299 (61.9)	43 (17.8)	9 (3.7)
AEs leading to discontinuation	83 (17.2)	48 (10)	15 (6.2)	10 (4.1)
Suspected drug-related	68 (14.1)	37 (7.7)	8 (3.3)	4 (1.7)
AEs requiring dose interruption/change	361 (74.7)	305 (63.2)	55 (22.8)	23 (9.6)
Suspected drug-related	330 (68.3)	284 (58.8)	25 (10.4)	9 (3.7)
AEs requiring additional therapy	420 (87.0)	174 (36)	189 (78.4)	48 (20)
Suspected drug-related	295 (61.1)	93 (19.3)	67 (27.8)	4 (1.7)

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MONALEESA-2	RIBO+NSAI(LET) (N=334)		PBO+NSAI(LET) (N=330)	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
All deaths	34 (10.2)	-	33 (10.0)	-
On-treatment deaths	6 (1.8)	-	1 (0.3)	-
AEs	330 (98.8)	279 (83.5)	322 (97.6)	115 (34.8)
Suspected drug-related	322 (96.4)	249 (74.6)	257 (77.9)	30 (9.1)
Serious AEs	78 (23.4)	64 (19.2)	45 (13.6)	31 (9.4)
Suspected drug-related	27 (8.1)	24 (7.2)	5 (1.5)	3 (0.9)
AEs of special interest	323 (96.7)	247 (74)	238 (72.1)	40 (12.1)
Suspected drug-related	308 (92.2)	230 (68.9)	131 (39.7)	13 (3.9)
AEs leading to discontinuation	52 (15.6)	39 (11.7)	12 (3.6)	6 (1.8)
Suspected drug-related	45 (13.5)	32 (9.6)	7 (2.1)	1 (0.3)
AEs requiring dose interruption/change	252 (75.4)	220 (65.9)	56 (17.0)	20 (6.1)
Suspected drug-related	235 (70.4)	209 (62.6)	27 (8.2)	9 (2.7)
AEs requiring additional therapy	302 (90.4)	120 (35.9)	279 (84.5)	71 (21.5)
Suspected drug-related	219 (65.6)	66 (19.8)	125 (37.9)	18 (5.5)
BOLERO-2	EVE+EXE (N=482)		PBO+EXE (N=238)	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
All deaths	83 (17.2)	NR	54 (22.7)	NR
On-treatment deaths	18 (3.7)	NR	4 (1.7)	NR
AEs	482 (100)	239 (49.6)	215 (90.3)	65 (27.3)
Suspected drug-related	465 (96.5)	185 (38.4)	148 (62.2)	19 (8.0)
Serious AEs	129 (26.8)	NR	33 (13.9)	NR
Suspected drug-related	54 (11.2)	NR	4 (1.7)	NR
AEs of special interest	456 (94.6)	NR	111 (46.6)	NR
Suspected drug-related	327 (88.6)	NR	48 (20.2)	NR
AEs leading to discontinuation	114 (23.7)	NR	12 (5.0)	NR
Suspected drug-related	93 (19.3)	NR	8 (3.4)	NR
AEs requiring dose interruption/change	303 (62.9)	NR	34 (14.3)	NR
AEs requiring additional therapy	450 (93.4)	NR	170 (71.4)	NR

CI = confidence interval; n = number of participants reporting data; N = total participants in group; AE, adverse event; FULV= fulvestrant; PBO= placebo; RIBO= ribociclib; SAE= serious adverse event; EVE= everolimus; EXE= exemestane; NR= not reported; LET= letrozole; NSAI= non-steroidal aromatase inhibitor.

Source: Compiled during the evaluation based on Tables 2-35, 2-41, 2-47; pp 121,127, 133 of the submission.

- 6.32 The total number of adverse events was slightly higher in the RIBO+FULV arm of MONALEESA-3 compared with PBO+FULV (99.2% minus 95.9%= +3.3%). However, a substantial difference was seen in the total number of ≥Grade 3 events for RIBO+FULV (+48.8%). The difference in the proportion of ≥Grade 3 serious AEs (+9.5%) and ≥Grade 3 AEs leading to discontinuation (+5.9%) was also higher in the RIBO+FULV arm.
- 6.33 Compared with PBO+NSAI, the active treatment arm in MONALEESA-2, RIBO+NSAI, led to a higher number of Grade 3/4 total adverse events (+48.7%), serious AEs (+9.8%), and AEs leading to discontinuation (+9.9%).
- 6.34 Similarly, in BOLERO-2, more patients in the intervention arm (EVE+EXE) experienced Grade 3/4 total adverse events (+22.3%). Information about Grade 3/4 serious AEs and AEs leading to discontinuation was not provided for BOLERO-2.

Indirect comparison of safety

- 6.35 The submission used an unadjusted indirect comparison to compare adverse events associated with the RIBO+FULV arm of MONALEESA-3 with those in the RIBO+NSAI and EVE+EXE arms of the MONALEESA-2 and BOLERO-2 trials, respectively. The submission stated that the main emphasis was on Grade 3 and 4 AEs that occurred at a rate of $\geq 2\%$ in the intervention arms of the three main trials. AEs were not analysed by the line of therapy as these data were not available.

First-line setting

- 6.36 For the first-line treatment setting, a summary of the comparison of the incidence of AEs between RIBO+FULV in MONALEESA-3 with RIBO+NSAI in MONALEESA-2 is presented in Table 10.
- 6.37 Although the Grade 3/4 AE profile of RIBO+FULV was generally like that of RIBO+NSAI, neutropenia (-7.3%), nausea (-0.9%), vomiting (-2.1%), leukopenia (-3.1%), hypertension (-6.8%) and decreased WBC count (-5.8%) were slightly lower in the RIBO+FULV group. Conversely, anaemia (+1.6%) and increased ALT levels (+0.3%) were slightly higher in the RIBO+FULV group.
- 6.38 The submission claimed non-inferior safety for RIBO+FULV compared to RIBO+NSAI for the first-line treatment setting based on absolute differences between the incidences of adverse events. No formal non-inferiority analyses of safety were performed. However, informally, the incidence of adverse events appear similar between the two treatments.

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Table 10: Results of unadjusted indirect comparison of individual AEs: RIBO+FULV vs RIBO+NSAI- FIRST LINE

Adverse event	Grade	MONALEESA 3	MONALEESA-2	Percent difference %
		RIBO+FULV	RIBO+NSAI	
Neutropenia	Grade 3	36.6%	41.0%	-4.4%
	Grade 4	5.8%	8.7%	-2.9%
Nausea	Grade 3	1.4%	2.4%	-0.9%
	Grade 4	0.0%	0.0%	0.0%
Vomiting	Grade 3	1.4%	3.6%	-2.1%
	Grade 4	0.0%	0.0%	0.0%
Back pain	Grade 3	1.7%	2.7%	-1.0%
	Grade 4	0.0%	0.0%	0.0%
Neutrophil count decreased	Grade 3	13.3%	14.4%	-1.1%
	Grade 4	1.0%	0.9%	0.1%
Anaemia	Grade 3	3.1%	1.2%	1.9%
	Grade 4	0.0%	0.3%	-0.3%
Leukopenia	Grade 3	5.2%	8.1%	-2.9%
	Grade 4	0.4%	0.6%	-0.2%
Increased ALT	Grade 3	6.6%	7.8%	-1.2%
	Grade 4	1.9%	1.8%	0.1%
Increased AST	Grade 3	4.8%	4.8%	0.0%
	Grade 4	1.2%	0.9%	0.3%
Hypertension	Grade 3	4.1%	10.8%	-6.6%
	Grade 4	0.2%	0.0%	0.2%
Decreased WBC count	Grade 3	7.0%	12.3%	-5.2%
	Grade 4	0.0%	0.6%	-0.6%

ALT= alanine aminotransferase; AST= aspartate aminotransferase; FULV= fulvestrant; NSAI= non-steroidal aromatase inhibitor; RIBO= ribociclib; WBC= white blood cell. Note:

Source: Table 2-68, p166 of the submission.

Note that the results presented in MAIC are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for MONALEESA-2 or MONALEESA-3. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Second-line

6.39 For the second-line treatment setting, a summary of the comparison of incidence of AEs between RIBO+FULV in MONALEESA-3 with EVE+EXE in BOLERO-2 is presented in Table 11.

Table 11: Results of unadjusted indirect comparison of individual AEs: RIBO+FULV vs EVE+EXE- SECOND LINE

Adverse event	Grade	MONALEESA 3	BOLERO-2	Percent difference (%)
		RIBO+FULV500	EVE+EXE	
Neutropenia	Grade 3	36.6%	2.3%	34.4%
	Grade 4	5.8%	0.0%	5.8%
Neutrophil count decreased	Grade 3	13.3%	0.0%	13.3%
	Grade 4	1.0%	0.0%	1.0%
Decreased WBC count	Grade 3	7.0%	0.0%	7.0%
	Grade 4	0.0%	0.0%	0.0%
Leukopenia	Grade 3	5.2%	0.4%	4.8%
	Grade 4	0.4%	0.0%	0.4%
Increased ALT	Grade 3	6.6%	3.1%	3.5%
	Grade 4	1.9%	0.2%	1.7%
Increased AST	Grade 3	4.8%	3.1%	1.6%
	Grade 4	1.2%	0.2%	1.0%
Stomatitis	Grade 3	0.4%	7.9%	-7.5%
	Grade 4	0.0%	0.0%	0.0%
Hyperglycaemia	Grade 3	0.4%	5.0%	-4.6%
	Grade 4	0.0%	0.4%	-0.4%
Anaemia	Grade 3	3.1%	6.6%	-3.5%
	Grade 4	0.0%	0.6%	-0.6%
Pneumonitis	Grade 3	0.0%	3.1%	-3.1%
	Grade 4	0.0%	0.0%	0.0%
Dyspnoea	Grade 3	1.2%	4.1%	-2.9%
	Grade 4	0.2%	0.2%	0.0%
Thrombocytopenia	Grade 3	0.6%	2.1%	-1.5%
	Grade 4	0.2%	0.8%	-0.6%

ALT= alanine aminotransferase; AST= aspartate aminotransferase; FULV= fulvestrant; EVE= everolimus; EXE= exemestane; RIBO= ribociclib; WBC= white blood cell.

Note: Grade 3-4 AEs are shaded in grey.

Source: Table 2-69, p167 of the submission.

Note that the results presented in MAIC are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for MONALEESA-2 or MONALEESA- 3. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.40 Overall, AEs trended higher for RIBO+FULV compared with EVE+EXE. Incidences of Grade 3/4 AEs that were higher in the RIBO+FULV group included neutropenia (+40.2%), neutrophil count decreased (+14.3%), decreased WBC count (+7.0%), leukopenia (5.2%), and increased liver enzymes (+7.8%). Conversely, stomatitis (-7.5%), hyperglycaemia (-5.0%), anaemia (-4.1%), pneumonitis (-3.1%), dyspnoea (-2.9%), and thrombocytopenia (-2.1%) were comparatively lower in the RIBO+FULV group.

Benefits/harms

6.41 The indirect nature of the comparisons presented in the submission did not allow for a reliable comparison of the benefits and harms of RIBO+FULV vs RIBO+NSAI and EVE+EXE. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.42 The submission described the effectiveness of RIBO+FULV as non-inferior compared with RIBO+NSAI for first-line treatment. The ESC considered that the results of the unanchored MAIC supported non-inferiority for the endpoint of PFS: HR=0.92 (95% CI: 0.72, 1.12) given the similar trial populations in MONALEESA-2 and MONALEESA-3. However, the ESC noted that the OS data from MONALEESA-2 and MONALEESA-3 were immature; in MONALEESA-3 (whole trial population) 37.9 % of patients had died at the second data-cut and in MONALEESA-2 (whole trial population) only 17.4% of patients had died at the second data-cut. The confidence intervals from the unanchored MAIC were wide (HR for OS: 1.08 (95% CI: 0.73, 1.60)). The upper 95% confidence limit of the OS hazard ratio of 1.6 exceeded the claimed non-inferiority margin of 1.4. The PSCR noted that the PBAC's acceptance of non-inferiority of palbociclib and abemaciclib to ribociclib were based on non-inferior PFS.
- 6.43 The submission described the safety of RIBO+FULV as non-inferior compared with RIBO+NSAI. The number of adverse events for patients treated with RIBO+FULV was comparable to RIBO+NSAI and the ESC considered it was reasonable to conclude that safety was similar.
- 6.44 The PBAC considered that the claim of non-inferior comparative effectiveness in the first line setting was reasonable.
- 6.45 The PBAC considered that the claim of non-inferior comparative safety in the first line setting was reasonable.
- 6.46 The submission described the effectiveness of RIBO+FULV as superior compared with EVE+EXE for second line treatment. The ESC considered that a mix of other treatments such as chemotherapy (e.g. capecitabine) and endocrine therapies (e.g. tamoxifen) could also be considered comparators for some patients in second-line and subsequent-lines (noting that the PBS restriction would allow use in subsequent lines).
- 6.47 The ESC considered that it was unclear whether the unanchored MAIC in the second-line setting was unbiased given baseline imbalances between the MONALEESA-3 and BOLERO 2 subgroups (e.g. in terms of age, proportion of patients with visceral disease and number of metastatic sites involved). While weighting may have corrected for these factors, the ESC considered that the baseline imbalances indicated that the patient populations were substantially different. The true uncertainty in the PFS and OS hazard ratios is likely to be much greater than reported in the submission due to imbalances in prognostic factors that were not accounted for. Further, adjustments to reduce the heterogeneity between the trial populations (i.e. inclusion of the second-line subgroup only) substantially reduced the size of the population available for analysis (e.g. it was based on 100 patients in the RIBO+FULV arm). Overall, the ESC considered that the unanchored MAIC in the second-line setting may not be sufficiently reliable for decision-making purposes.

- 6.48 The submission described RIBO+FULV as superior in terms of safety compared with EVE+EXE. The number of adverse events in RIBO+FULV were slightly higher than EVE+EXE in second-line. However, the ESC considered that the claim of superior safety might be reasonable as the majority of the grade 3 adverse events related to ribociclib were haematological and asymptomatic, and in clinical practice RIBO+FULV seems to be better tolerated than EVE+EXE.
- 6.49 The PBAC considered that the claim of superior comparative effectiveness in the second-line treatment setting was supported, however, the magnitude of benefit for RIBO+FULV over EVE+EXE was highly uncertain given the potential for bias in the unanchored MAIC.
- 6.50 The PBAC considered that the claim of superior comparative safety versus EVE+EXE was based on limited clinical data but appeared clinically reasonable.

Economic analysis

Cost-minimisation analysis (RIBO+FULV versus RIBO+NSAI)

- 6.51 The submission presented a cost-minimisation analysis comparing RIBO+FULV to RIBO+NSAI as first line treatment for HR+ HER2- advanced breast cancer. This was consistent with the clinical claim of non-inferior efficacy and safety.
- 6.52 For the cost-minimisation analysis, the submission relied on the results of the unanchored MAIC to support the claim that PFS and OS with RIBO+FULV was non-inferior to RIBO+NSAI. The ESC considered that non-inferiority was only supported for the outcome of PFS; for the outcome of OS, based on a non-inferiority margin of 1.4, non-inferiority was not adequately demonstrated in the submission.
- 6.53 The submission estimated the equi-effective doses as:
- ribociclib 511 mg daily for 21 days of a 28- day cycle with fulvestrant 500mg once every 28 days plus fulvestrant 500 mg loading dose at day 14; and
 - ribociclib 511 mg daily for 21 days of a 28-day cycle with letrozole 2.5 mg once daily.
- 6.54 The dose of ribociclib, when used in combination with either fulvestrant or NSAI, was calculated based on a relative dose intensity of 85.2%. This estimate was sourced from the relative dose intensity of ribociclib when used with fulvestrant in the MONALEESA-3 trial. The relative dose intensity of ribociclib when used with letrozole in MONALEESA-2 was 80.1%. The commentary noted that using trial-based relative dose intensities would have increased the total cost of RIBO+FULV compared to ribociclib + letrozole. The ESC and the PBAC considered that there did not appear to be a clinical reason why dose intensities for ribociclib would differ depending its combination with fulvestrant or NSAI, given the similar safety profiles of RIBO+FULV and RIBO+NSAI but noted the results of the trials and that inclusion of the trial-based RDIs would reduce the AEMP for ribociclib by 7.5%.

- 6.55 The submission did not consider the duration of treatment with ribociclib. The mean duration of treatment with ribociclib (with fulvestrant) in MONALEESA-3 was 13.33 months, while the mean duration of treatment with ribociclib (with letrozole) in MONALEESA-2 was 11.8 months. However, this was based on a longer duration of follow-up in MONALEESA-3 (39.4 months versus 26.3 months in MONALEESA-2). The mean duration of treatment with RIBO+FULV and RIBO+NSAI is uncertain as both MONALEESA-3 and MONALEESA-2 are ongoing. The ESC considered that it was not clear whether there would be expected to be a difference in treatment duration for RIBO+FULV compared with RIBO+NSAI.
- 6.56 The submission assumed a mean duration of therapy with fulvestrant of 13.2 months, sourced from the MONALEESA-3 trial. The modelled cost of the fulvestrant loading dose (\$████) was divided by 13.2 months (14.3 cycles) to calculate a per-cycle cost for the analysis. The cost of the fulvestrant loading dose should be \$████ (proposed AEMP for fulvestrant). The base case was re-specified to correct this error.
- 6.57 The cost-minimisation analysis also considered the costs of administering fulvestrant, monitoring and adverse events. This was reasonable, however, the ESC noted that the administration cost used was for administration by a nurse practitioner (MBS item 82200), which may not be applicable in this setting.
- 6.58 The results of the cost-minimisation are presented in Table 12.

Table 12: Results of the cost-minimisation analysis

Component	RIBO+FULV	RIBO+NSAI	Difference
Medicine costs (28-day cycle)			
Ribociclib, AEMP (at current price) • With relative dose intensity (85.2%)	\$████	\$████	\$████
Fulvestrant, AEMP	\$████	\$0.00	\$████
Fulvestrant loading dose, AEMP	\$████ ^a	\$0.00	\$████ ^a
NSAI	\$0.00	\$15.66	-\$15.66
Additional costs (28-day cycle)			
Administration	\$9.75	\$0.00	\$9.75
Administration loading dose	\$0.68	\$0.00	\$0.68
Monitoring	\$35.06	\$66.97	-\$31.91
Adverse events	\$0.09	\$0.23	-\$0.13
Total cost per cycle	\$████^a	\$████	\$████^a
Price of ribociclib required for cost-minimisation (no net difference in total cost per cycle)			
Ribociclib, AEMP (proposed)	\$████ \$████ (corrected) ^a		

Source: Table 3-6, p185 of the submission. Italicised values calculated during the evaluation to correct the price of fulvestrant.

RIBO+FULV = ribociclib + fulvestrant; RIBO+NSAI = ribociclib + non-steroidal aromatase inhibitor.

^a The model incorrectly listed the cost of the fulvestrant loading dose as \$████. When corrected to \$████, the per-cycle cost becomes \$████

- 6.59 The submission concluded that the 28-day treatment cost of RIBO+FULV will be \$████ higher than RIBO+NSAI. Thus, the submission noted that a price reduction would be required for ribociclib when used in combination with fulvestrant as first line treatment. As such, the proposed effective AEMP for ribociclib 600 mg dose in this setting was \$████. This was corrected to \$████ in the evaluation.

6.60 The cost-minimisation analysis was based on the current AEMP of ribociclib (in its current listing for use in combination with NSAID). However, in its March 2018 recommendation of ribociclib, the PBAC considered that the cost-effectiveness of ribociclib (in that setting) could be improved “via a reduction in price in conjunction with financial caps” (Para 6.1, ribociclib PSD, March 2019). The PBAC noted that at the time of recommending ribociclib, the caps were intended to be exceeded by 27% to achieve cost-effective net pricing. Thus, the PBAC considered that the comparator price for currently listed ribociclib (for use in combination with NSAID) applied in the cost-minimisation analysis should take into account the effective price that was intended for RIBO+NSAID including both the effective price and the intended RSA rebate for breaching the subsidisation caps.

Cost-effectiveness analysis (RIBO+FULV versus EVE+EXE)

6.61 The submission presented a cost-effectiveness analysis comparing RIBO+FULV to EVE+EXE as second line treatment for HR+ HER2- advanced breast cancer, using the results from the unanchored MAIC in the base case.

6.62 Table 13 summarises the key components of the economic evaluation for second line therapy.

Table 13: Summary of model structure for second line treatment, key inputs and rationale

Component	Summary
Treatments	Ribociclib + fulvestrant (RIBO+FULV) vs everolimus + exemestane (EVE+EXE)
Time horizon	10 years in the model base case vs. 3.5 years in MONALEESA-3 (RIBO+FULV) and 2.3 years in BOLERO-2 (EVE+EXE)
Outcomes	Life years gained and QALYs gained
Methods used to generate results	Partitioned survival model
Health states	Three health states (pre-progression survival, post-progression survival, dead). Pre-progression survival is stratified by on/off treatment.
Cycle length	28 days
Allocation to health states	RIBO+FULV: Progression free survival (PFS) and overall survival (OS) are from the MONALEESA-3 trial, unanchored MAIC. Pre-progression survival on/off treatment is derived from time to treatment discontinuation (TTD) in MONALEESA-3, unanchored MAIC. EVE+EXE: PFS and OS are hazard ratios from unanchored MAIC, applied to PFS and OS for RIBO+FULV. Pre-progression survival on/off treatment is derived from PFS for RIBO+FULV in MONALEESA-3, unanchored MAIC, with two hazard ratios used to convert to PFS for EVE+EXE, then to TTD for EVE+EXE.
Extrapolation method	Parametric models fitted to RIBO+FULV arm with exponential selected in the base case for PFS and OS, and Weibull selected in the base case for TTD, based on goodness of fit and clinical plausibility. For the EVE+EXE arm, hazard ratios were applied to the RIBO+FULV parametric models. Extrapolation was applied for the duration of the model; no observed trial data were used in the base case. 53% of incremental QALYs and 31% of incremental costs occur in the extrapolated period (after 3.5 years).
Health related quality of life	Pre-progression survival on/off treatment from MONALEESA-3 trial. Post-progression survival from Lloyd (2006) Pre-progression survival on treatment = 0.766; Pre-progression survival off treatment = 0.778; Post-progression survival = 0.505

Source: Table 3-7, p188 of the submission and CEA Model workbook.

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EVE+EXE = everolimus + exemestane; IPD = individual patient data; OS = overall survival; PFS = progression-free survival; PPS = post progression survival; QALY = quality adjusted life year; RIBO+FULV = ribociclib + fulvestrant; TTD = time to treatment discontinuation

- 6.63 PFS and OS for RIBO+FULV were extrapolated using exponential functions. No observed trial data were applied in the model.
- 6.64 PFS and OS for EVE+EXE were estimated by applying hazard ratios to the PFS and OS distributions in the RIBO+FULV arm based on the results of the unanchored MAIC (as shown in the table below). The ICER is sensitive to the PFS and OS hazard ratios applied. The test of linearity of the Schoenfeld residuals was not statistically significant, suggesting the proportional hazards assumption was appropriate. However, the evaluation considered that PFS and OS for the EVE+EXE arm could also have been extrapolated from the adjusted Kaplan-Meier graphs.

Table 14: Survival distributions applied in the economic evaluation

	Survival Distribution	Hazard Ratio
RIBO+FULV		
PFS	Exponential – RIBO+FULV PFS	1.00
OS	Exponential – RIBO+FULV OS	1.00
TTD - RIBO	Weibull – RIBO+FULV TTD	1.00
TTD - FULV	Exponential – RIBO+FULV TTD	1.00
EVE+EXE (from unanchored MAIC in the second-line setting)		
PFS	Exponential – RIBO+FULV PFS	2.52
OS	Exponential – RIBO+FULV OS	1.78
TTD – EVE	Exponential – RIBO+FULV PFS	3.20
TTD – EXE	Exponential – RIBO+FULV PFS	3.20

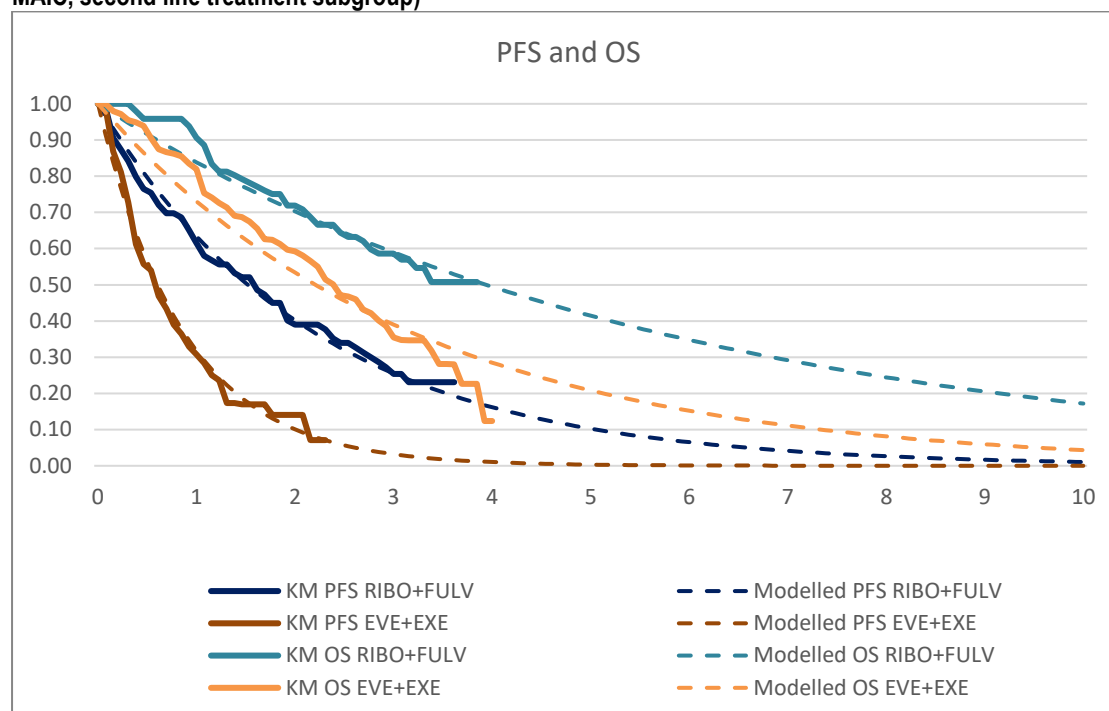
Source: Table 2-66, p161 of the submission, pp195-198 of the submission, and sheet Regimens_DISC of CEA Model workbook.

EVE+EXE = everolimus + exemestane; OS = overall survival; PFS = progression-free survival; RIBO+FULV = ribociclib + fulvestrant; TTD = time to treatment discontinuation.

^a TTD hazard ratio for EVE+EXE was calculated by multiplying the hazard ratio for PFS (EVE+EXE vs RIBO+FULV = 2.52) by the EVE+EXE hazard ratio for TTD vs PFS (1.27) ($2.52 * 1.27 = 3.20$)

- 6.65 Figure 4 presents modelled PFS and OS for RIBO+FULV and EVE+EXE over the 10-year time horizon and Kaplan-Meier data from the unanchored MAIC. OS for EVE+EXE is modelled using an exponential function which provides a poor visual fit to the observed data, underestimating survival for the trial period until median OS in BOLERO-2 (which favours RIBO+FULV). The ESC considered that the extrapolated function for OS for EVE+EXE had poor visual fit to the observed data but noted that the ICER was relatively insensitive to the choice of extrapolation function. Modelled estimates of PFS and OS for EVE+EXE are likely to have been higher if extrapolated from observed trial data, increasing the ICER.

Figure 4: Observed and modelled PFS and OS for patients treated with RIBO+FULV and EVE+EXE (unanchored MAIC, second line treatment subgroup)



Source: Compiled during the evaluation from CMA Model workbook. Kaplan-Meier data for EVE+EXE in Effectiveness Analysis 2 (after MAIC adjustment) were digitised from Figure 2-23, p161 of the submission. EVE+EXE = everolimus + exemestane; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; RIBO+FULV = ribociclib + fulvestrant

- 6.66 Based on the extrapolated OS, 17% of patients in the RIBO+FULV arm and 5% of patients in the EVE+EXE arm were still alive at the 10 year time horizon.
- 6.67 Modelled outcomes for EVE+EXE are not consistent with the clinical data provided. Compared with MAIC-adjusted data, the model underestimates median OS for EVE+EXE by 1.5 months (Table 15). As median OS has not been reached for MONALEESA-3, no comparison can be made for RIBO+FULV.
- 6.68 The submission did not provide time to discontinuation results from the unanchored MAIC. Therefore, it was unclear whether modelled time to discontinuation was reliable compared with the clinical data.

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Table 15: Median PFS, OS and TTD for patients treated with RIBO+FULV and EVE+EXE, unanchored MAIC, second line treatment subgroup

Median Outcome	PFS (months)	OS (months)
RIBO+FULV		
Trial (median 39.4 months follow-up ^a)	18.8	NE
Model (10-year time horizon)	18.4	46.9
Difference (modelled – observed)	-0.4	NE
EVE+EXE		
Trial (median 17.7 months follow-up ^b)	6.7	28.2
Model (10-year time horizon)	7.4	26.7
Difference (modelled – observed)	0.7	-1.5

Source: Table 3-19, p209 of the submission; p160 of the submission; CUA Model workbook; Table 14.3-1.1, p12323 of MONALEESA-3 CSR; Table 12-1, p154 of BOLERO-2 CSR.

EVE+EXE = everolimus + exemestane; NE = not evaluable; NR = not reached; OS = overall survival; PFS = progression free survival; RIBO+FULV = ribociclib + fulvestrant; TTD = time to discontinuation.

^a MONALEESA-3 June 2019 data cut; ^b BOLERO-2 December 2011 data cut

6.69 The PBAC considered that the disease management costs applied in the PFS and PPS health states appeared to be underestimated because the submission assumed that:

- patients in PFS off treatment receive no follow-up care; and
- the only disease management cost applied in the PPS health state was a monthly consultation with an oncologist (MBS item 105, \$44.35). This estimate of resource utilisation is lower than that presented in the RIBO+NSAI submission (which estimated PPS health state costs of \$212.70 per month for patients in second and later lines).

The PBAC noted that applying higher disease management increased the ICER slightly.

6.70 The submission incorrectly calculated the DPMQ of fulvestrant (\$██████) from a proposed AEMP of \$████. The correct DPMQ for fulvestrant is \$████. The submission did not include an initial and loading dose of fulvestrant in the first model cycle. During the evaluation, the base case was respecified to correct these two issues. The ICER then increased slightly, from \$55,000 to < \$75,000 to \$55,000 to < \$75,000 per QALY.

6.71 Table 16 presents the key drivers of the economic model.

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Table 16: Key drivers of the model

Description	Method/Value	Impact Base case: \$55,000 to < \$75,000/QALY
Trial data analysis	Modelled gains in PFS and OS are based on hazard ratios derived from the unanchored MAIC in the second-line setting. The model is highly sensitive to changes in the PFS and OS hazard ratios.	Highly uncertain
Modelled OS benefit	Median survival for RIBO+FULV in MONALEESA-3 had not been reached with only 42% of patients having died (in the second-line population) at the June 2019 data-cut. The median modelled OS gain of 20.2 months is uncertain.	Uncertain
Extrapolation	PFS, OS and time on treatment are estimated using parametric functions for the duration of the model. The ESC considered that the observed time to event data from the trials should have been used up to the time point at which the observed data became unreliable as a result of small numbers of patients remaining event-free.	Moderate, favours RIBO+FULV Incorporating Kaplan-Meier data until median PFS/OS increased the ICER to \$55,000 to < \$75,000/QALY gained

Source: Table 3-15, p205 of the submission; pp 148, 160, 192, 195, 197 of the submission; sheets 'Costs_Drug' and 'Regimens_Dose' of CEA model workbook.

DPMQ = dispensed price maximum quantity; EVE+EXE = everolimus + exemestane; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; RIBO+FULV = ribociclib + fulvestrant

6.72 The submission did not present a stepped analysis. The results of the economic evaluation are presented in Table 17.

Table 17: Results of the economic evaluation – respecified base case

	RIBO+FULV	EVE+EXE	Increment
Costs	\$ [redacted]	\$52,894	\$ [redacted]
	\$ [redacted]	\$52,894	\$ [redacted]
Life years	[redacted]	[redacted]	1.33
QALYS	[redacted]	[redacted]	0.96
Incremental cost per life year gained			\$ [redacted]
Incremental cost per QALY gained			\$ [redacted]

Source: Table 3-24, p212 of the submission. Italicised numbers calculated during the evaluation using the corrected DPMQ of fulvestrant and including initial + loading dose of fulvestrant in cycle 1.

EVE+EXE = everolimus + exemestane; QALY = quality adjusted life year; RIBO+FULV = ribociclib + fulvestrant

The redacted table shows ICERs in the range of \$35,000 to < \$45,000 per life year gained; and \$55,000 to < \$75,000 per QALY gained.

6.73 The results of key sensitivity analyses are summarised in the table below.

6.74 The ICER is most sensitive to the hazard ratios applied to estimate EVE+EXE in PFS and OS. Using the results of the naïve indirect comparison (hazard ratios from the unanchored MAIC, unweighted in table below), the ICER increases from \$55,000 to < \$75,000 to \$55,000 to < \$75,000 per QALY. Using the PFS and OS results from the multiple-stepwise indirect comparison (Analysis 1) the ICER increased to \$155,000 to < \$255,000 per QALY. The ESC considered that all ICERs, including the base case ICER, are extremely uncertain as they are based on comparisons of clinical trial data from distinctly different patient populations.

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- 6.75 The ESC considered that the 10 year time horizon may be too long, given that the results used were based on the extrapolation of data from an unanchored MAIC with a high level of uncertainty. The ESC considered that 7 years would be more appropriate to use in the base case of the model and noted that this would increase the ICER to \$55,000 to < \$75,000. The pre-PBAC response noted that in the model, 30% of patients remain alive at seven years. The PBAC noted that RIBO+NSAI was recommended on the basis of a model with a 7 year time horizon, reflecting uncertainty in the long term survival outcomes for RIBO+NSAI.
- 6.76 No observed trial data were applied in the model. The ESC considered that the observed time to event data from the trials should have been used up to the time point at which the observed data became unreliable as a result of small numbers of patients remaining event-free, consistent with the PBAC Guidelines (paragraph 3A.4.3). The ESC noted that using observed data until median PFS and OS increased the ICER to \$55,000 to < \$75,000 per QALY. The pre-PBAC response disagreed with the evaluation’s approach and presented a scenario which used the trial data up to the point of median survival (27 months) and calculated a new OS distribution, applied after the point of median survival. The PBAC considered that recalculating the survival distribution based on the remainder of the data after median follow-up (i.e. data that were more likely to be censored or unreliable) was not appropriate and considered the evaluation’s approach was reasonable.

Table 18: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case (respecified)^a	\$ [REDACTED]	0.96	\$ [REDACTED]
7 year time horizon (base case: 10 years)	\$ [REDACTED]	0.80	\$ [REDACTED]
Include KM data to median PFS and OS	\$ [REDACTED]	0.87	\$ [REDACTED]
Hazard ratio PFS (base case 2.52)			
2.20 (unanchored MAIC, unweighted) ^b	\$ [REDACTED]	0.93	\$ [REDACTED]
1.19 (Effectiveness Analysis 1, multiple-stepwise indirect comparison) ^c	\$ [REDACTED]	0.72	\$ [REDACTED]
Hazard ratio OS (base case 1.78)			
1.67 (unanchored MAIC, unweighted) ^d	\$ [REDACTED]	0.89	\$ [REDACTED]
1.20 (Effectiveness Analysis 1, multiple-stepwise indirect comparison) ^e	\$ [REDACTED]	0.52	\$ [REDACTED]
Multivariate analyses			
Hazard ratio PFS and OS from unanchored MAIC, unweighted ^{b,d}	\$ [REDACTED]	0.86	\$ [REDACTED]
PFS and OS hazard ratios from Effectiveness Analysis 1, multiple-stepwise indirect comparison ^{c,e}	\$ [REDACTED]	0.28	\$ [REDACTED]

Source: Table 3-25, pp214-216 of the submission. Conducted during the evaluation.

ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; PFS = progression free survival; OS = overall survival; QALY = quality adjusted life year.

^a change cells E17 & E18 in sheet 'Costs_Drug' to \$ [REDACTED], delete value in cell J15, sheet 'Regimens_Dose'; ^b change cell Q21 in sheet 'Efficacy_PFS' to 0.454; ^c change cell Q21 in sheet 'Efficacy_PFS' to 0.84; ^d change cell O19 in sheet 'Efficacy_PPS_OS' to 0.600; ^e change cell O19 in sheet 'Efficacy_PPS_OS' to 0.83;

The redacted table shows ICERs in the range of \$55,000 to < \$75,000/QALY, \$75,000 to < \$95,000/QALY, \$95,000 - < \$115,000/QALY, and \$155,000 to < 255,000/QALY.

Drug cost/patient/course

6.77 Table 19 compares the drug cost per patient per course of first line treatment for RIBO+FULV and RIBO+NSAI in MONALEESA-3, MONALEESA-2, the cost-minimisation analysis and financial estimates. Trial dose and duration apply dosing information from the safety population sets (first and second line treatments) as information specific to first line patients were not provided in the submission. The pre-PBAC response amended the duration of RIBO+FULV therapy in the financial estimates from 30.0 months to 20.2 months, which would lower the drug cost/patient/course of RIBO+FULV in the financial estimates (table not updated to reflect this change).

Table 19: Drug cost per patient for proposed and comparator drugs – first line (as estimated in the submission)

	RIBO+FULV			RIBO+NSAI		
	Trial dose and duration	CMA	Financial estimates	Trial dose and duration	CMA	Financial estimates
Mean daily dose (on treatment days)	R: 512.5 mg ^a F: 511.2 mg ^a + 500mg loading	R: 511.0 mg ^b F: 500 mg + 500mg loading	R: 510.0 mg ^c F: 500 mg + 500mg loading	R: 482.9 mg ^a L: 2.5 mg ^a	R: 511.0 mg ^b L: 2.5 mg	R: 510.0 mg ^c L: 2.5 mg
Mean duration (months)	R: 12.11 F: 13.15	Not considered	30.0	R: 10.9 L: 11.8	Not considered	25.3
Cost/patient/course	\$ [REDACTED] (based on truncated means)	Not calculated	\$ [REDACTED]	\$ [REDACTED] (based on truncated means)	Not calculated	\$ [REDACTED]

Source: pp221-222 of the submission; CMA workbook; Section 4 workbook; Tables 12-1, 12-2 & 14.3-1.2, pp172-173 & 12324 of the MONALEESA-3 CSR, Tables 12-1 & 12-2, pp94-95 of the MONALEESA-2 CSR. Italicised values include adjusted price of fulvestrant and respecified price for ribociclib in the CMA.

CMA = cost minimisation analysis; F = fulvestrant; L = letrozole; R = ribociclib; RIBO+FULV = ribociclib + fulvestrant; RIBO+NSAI = ribociclib + non-steroidal aromatase inhibitor

^a mean daily dose = [mean total dose received] / {[mean duration (months), converted to 28-day cycles] / # dosing days per cycle}; ^b prescribed dose x 85.16% (relative dose intensity); ^c prescribed dose x 85.00% (relative dose intensity);

6.78 Table 20 compares the drug cost per patient per course of second line treatment for RIBO+FULV and EVE+EXE in MONALEESA-3, BOLERO-2, the economic evaluation and financial estimates. Trial dose and duration apply dosing information from the safety population sets (first and second line treatment). Trial dose and duration of treatment specific to second line patients were not provided in the submission. The pre-PBAC response amended the duration of RIBO+FULV therapy in the financial estimates from 18.8 months to 13.3 months, which would lower the drug cost/patient/course of RIBO+FULV in the financial estimates (table not updated to reflect this change).

Table 20: Drug cost per patient for proposed and comparator drugs – second line (as estimated in the submission)

	RIBO+FULV			EVE+EXE		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean daily dose (on treatment days)	R: 512.5 mg ^a F: 511.2 mg ^a + 500mg loading	R: 510.0 mg ^b F: 500.0 mg ^b + 500mg loading	R: 510.0 mg ^b F: 500.0 mg ^b + 500mg loading	EVE: 8.3 mg ^a EXE: 24.7 mg ^a	EVE: 7.9 mg ^b EXE: 24.5 mg ^b	EVE: 7.9 mg ^b EXE: 25 mg
Mean duration (months)	R: 12.11 F: 13.15	n/a	18.8	EVE: 4.55 EXE: 4.89	n/a	7.8
Cost/patient/ /course	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED] ^d	\$6,924	\$11,859	\$11,420

Source: Tables 12-1, 12-2 & 14.3-1.2, pp172-173 & 12324 of the MONALEESA-3 CSR, Tables 12-1 & 12-2, pp154-155 of the BOLERO-2 CSR, sheets 'Regimens_Dose', 'Comp1.Calc' & 'Comp5.Calc' of CEA Model workbook.

F = fulvestrant; EVE = everolimus; EXE = exemestane; R = ribociclib; RIBO+FULV = ribociclib + fulvestrant; TTD = time to treatment discontinuation

^a mean daily dose = [mean total dose received] / {[mean duration (months), converted to 28-day cycles] / # dosing days per cycle}; ^b mean daily dose = [prescribed daily dose] * [relative dose intensity]; ^c Amended during the evaluation to apply updated fulvestrant DPMQ and count loading and initial dose of fulvestrant in cycle 1; ^d Calculated during the evaluation using the proposed second line price for ribociclib and updated fulvestrant DPMQ.

Estimated PBS usage & financial implications

- 6.79 The submission used a combined epidemiological and market share approach to estimate four patient populations. Patients eligible for first line treatment were estimated using an epidemiological approach using data from the March 2018 PBAC RIBO+NSAI submission.
- 6.80 Population 1 (first line, patients substituting RIBO+FULV for CDKI+NSAI) was defined by a market share approach using PBS data for CDK4/6 inhibitors from 2018 to 2019. Population 2 (first line, growth of CDKI market) was defined by subtracting Population 1 from the eligible first line population. Population 3 (second line, patients displacing EVE+EXE) was defined by a market share approach using PBS data for everolimus from 2014 to 2019. Population 4 (second line, patients displacing EXE) was defined by subtracting Population 3 from patients not treated with chemotherapy in Population 2. The PBAC considered that many assumptions applied in this approach were unjustified and uncertain. The PBAC noted that the relative proportion of patients in first and subsequent line populations is important because it impacts on the weighted price for ribociclib.
- 6.81 Table 21 outlines the key inputs in the financial estimates.

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Table 21: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent population – HR+, HER2-advanced breast cancer, post-menopausal, ECOG status ≤1	3,527 in 2018 (IPSOS 2016)	Consistent with data presented in the RIBO+NSAI submission for a similar indication. The primary endocrine resistance restriction was removed for this submission
Growth of prevalent patients	6% (RIBO+NSAI submission)	Consistent with RIBO+NSAI submission
Growth of CDK4/6 market	19% in Year 1, 12% in year 2 to 6% in Years 3+ (no source provided)	Uncertain. DUSC considered annual market growth of up to 19% was unlikely to be observed as the market is expected to have stabilised.
Growth of everolimus market	0% in all years (no source provided)	Uncertain; PBS data provided with the submission suggests the market is contracting.
Uptake rate – Population 1	20% in Year 1 to 30% in Years 3+ (no source provided)	Uncertain
Uptake rate – Population 2	Chemotherapy: 10% in Year 1 to 20% in Year 6 (no source provided) NSAI: 0% in all years (no source provided)	Inconsistent with treatment algorithm presented in Section 1, where patients receiving chemotherapy are not suitable for treatment with CDK4/6 inhibitors. DUSC considered this was likely to be overestimated.
Uptake rate – Population 3	80% in Year 1 to 95% in Years 4+ (no source provided)	Uncertain. DUSC considered it is more likely that RIBO+FULV will add an additional line of therapy in this population and thus predicted cost savings will not be observed.
Uptake rate – Population 4	50% in all years (no source provided)	Uncertain. Assumes all patients who progress after first line NSAI receive exemestane and are suitable for substitution. Does not consider patients receiving chemo or best supportive care. DUSC considered that the estimated 50% of patients not fit for CDKi in the first line setting who are subsequently eligible for these agents in the second line setting is overestimated.
Duration of treatment – Population 1	RIBO+FULV: 30 months (changed to 20.2 months in the pre-PBAC response) RIBO+NSAI: 25.3 months	Mean duration of treatment in MONALEESA-3 was 13.3 months. Using median PFS for MONALEESA-2 is inappropriate. The pre-PBAC response updated the duration of therapy for the RIBO+FULV arm.
Duration of treatment – Population 2	RIBO+FULV: 30 months (changed to 20.2 months in the pre-PBAC response) Chemo: 12 months	Mean duration of treatment in MONALEESA-3 was 13.3 months. Assumption for chemo is not justified. The pre-PBAC response updated the duration of therapy for the RIBO+FULV arm.
Duration of treatment – Population 3	RIBO+FULV: 18.8 months (changed to 13.3 months in the pre-PBAC response) EVE+EXE: 7.8 months	Mean duration of treatment in MONALEESA-3 was 13.3 months, compared with 4.6 in BOLERO-2 for EVE+EXE. The pre-PBAC response updated the duration of therapy for the RIBO+FULV arm.
Duration of treatment – Population 4	RIBO+FULV: 18.8 months (changed to 13.3 months in the pre-PBAC response) EXE: 4.1 months	Mean duration of treatment in MONALEESA-3 was 13.3 months, compared with 5.0 months in BOLERO-2 for EVE. The pre-PBAC response updated the duration of therapy for the RIBO+FULV arm.
Compliance rate – ribociclib dose	200 mg/day: 10%, 400 mg/day: 25%, 600 mg/day: 65%, estimated based in 85% RDI from MONALEESA-3	This is uncertain. PBS data for CDK4/6 inhibitors used with NSAI suggest a RDI of 89%.
MBS items included	MBS item 66503 - blood lipids MBS item 66512 – liver function MBS item 66509 – serum electrolytes MBS item 65070 – complete blood count	Consistent with Section 3; frequency of bone densitometry monitoring for anastrozole, letrozole, and exemestane is uncertain. Including bone densitometry as monitoring for chemotherapy is inappropriate.

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Parameter	Value applied and source	Comment
	MBS item 11711 - electrocardiograph MBS Item 82200 – clinic nurse MBS item 12306 – bone densitometry	

Source: Tables 4-2, 4-3, 4-4, 4-5, 4-7, 4-9, 4-11 & 4-29, pp220-226 & 235-236 of the submission; p221 of the submission; Section 4 workbook; RIBO + NSAI Section 4 workbook, March 2018 PBAC submission.

6.82 Table 22 presents the estimated use and financial implications of listing RIBO+FULV, as estimated in the submission.

Table 22: Estimated use and financial implications (per the submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
First line treatment						
Number of patients treated						
Number of ribociclib scripts dispensed ^a						
Number of fulvestrant scripts dispensed ^b						
Second line treatment						
Number of patients treated						
Number of ribociclib scripts dispensed ^c						
Number of fulvestrant scripts dispensed ^b						
Estimated financial implications of RIBO+FULV						
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Estimated financial implications for offset medicines						
Number of ribociclib scripts offset						
Cost to PBS/RPBS less copayments	-\$	-\$	-\$	-\$	-\$	-\$
Net financial implications						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net cost to MBS	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to health budget	\$	\$	\$	\$	\$	\$

Source: Tables 4-14, 4-17, 4-25 & 4-29, pp228, 230-231 & 234-236 of the submission. Revised estimates include the corrected price of fulvestrant

^a Assuming 32.6 scripts per year for first line treatment as estimated by the submission.

^b Number of ribociclib scripts x (14.04/13.04). Workbook calculations include rounding.

^c Assuming 20.44 scripts per year for second line treatment per year as estimated by the submission.

6.83 The submission estimated that the total cost to the PBS/RPBS of listing RIBO+FULV would be \$50 million to < \$60 million in Year 6, and a total of \$200 million to < \$300 million in the first 6 years of listing. The pre-PBAC response proposed shorter durations of therapy for RIBO+FULV, which would reduce the financial impact.

6.84 DUSC considered the estimates presented in the submission to be significantly overestimated due to the issues outlined below.

6.85 The duration of treatment with RIBO+FULV presented in the financial estimates was not consistent with the trial evidence presented or the cost effectiveness model and appeared to be substantially overestimated. The duration of treatment specific to

first- and second-line therapy was not provided, and would have resulted in more certain estimates. DUSC considered that, given the data available, it would be more reliable to base the estimate on the treatment exposure in the clinical trial setting. DUSC suggested using the median treatment exposure of 20.2 months of letrozole + ribociclib in MONALEESA-2 for first line, and mean prescription duration of 13.3 months observed in MONALEESA-3 for second line estimates. This approach was accepted by the sponsor in the pre-PBAC response. The PBAC considered this was appropriate.

- 6.86 DUSC considered the estimated growth in the CDKI market was overestimated. This drug class has been PBS subsidised in Australia since July 2018 and the estimated annual market growth of up to 19% is unlikely to be observed as the market is expected to have stabilised. The pre-PBAC response disagreed that the market has stabilised, and stated that PBS statistics for CDKIs support the submission's estimated growth rates of 19% in 2021, 12% in 2022, and 6% in year from 2023 to 2026.
- 6.87 DUSC noted that growth in the utilisation of everolimus was assumed to be flat over the forward estimates period, but PBS Authorities data demonstrates that there has been a significant decrease in everolimus utilisation for breast cancer. Therefore DUSC considered that the projected offsets are likely to be overestimated.
- 6.88 Five different uptake rates were used across the four patient populations. DUSC considered that the uptake assumptions were highly uncertain and not adequately justified.
- Population 1 – DUSC considered that the uptake rate in population 1 was likely to be overestimated as patients may be hesitant to switch to a parenteral treatment.
 - Population 2 – the assumption of up to 20% uptake in patients currently receiving chemotherapy is likely to be overestimated as 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. Section 1 of the submission noted that patients receiving chemotherapy are those not considered suitable candidates for CDKI+NSAI or EVE+EXE (therefore unlikely to be suitable for RIBO+FULV), while Section 4 assumes all uptake in Population 2 is from chemotherapy patients. The submission assumed 0% uptake in patients receiving first line aromatase inhibitor monotherapy, which maximises the eligible second line population, which the PBAC considered was not reasonable.
 - Population 3 – the submission estimates displacement of EVE+EXE by up to 95% in year 4. This assumes that patients treated with RIBO+FULV will not receive EVE+EXE in subsequent lines of treatment. It is more likely that RIBO+FULV will add an additional line of therapy in this patient group and thus the predicted cost savings will not be observed.
 - Population 4 – the prevalent pool of patients with their disease controlled on first line endocrine therapy prior to July 2018 was likely to be underestimated. However, DUSC considered that the estimated 50% of patients not fit for CDKI in

the first line setting who are subsequently eligible for these agents in the second line setting was overestimated.

- 6.89 Grandfathered patients were not accounted for in the financial estimates.
- 6.90 The submission proposed a weighted price between the first and second-line settings of \$ [REDACTED] for the 600 mg dose (63 tablets per pack). The pre-PBAC response proposed revised durations of therapy in the first and second-line settings which resulted in a revised weighted price of \$ [REDACTED] which was based on:
- [REDACTED]% of total use of ribociclib (when used in combination with fulvestrant) would be in the first-line setting with an AEMP of \$ [REDACTED]
 - [REDACTED]% of total use of ribociclib (when used in combination with fulvestrant) would be in the second-line setting with an AEMP of \$ [REDACTED].

The PBAC noted that the revised weighted price remained higher than the current AEMP for ribociclib in its existing listing (\$ [REDACTED]).

Financial Management – Risk Sharing Arrangements

- 6.91 The submission considered that the population in the current submission extends beyond that previously negotiated for ribociclib and offered to work with the PBAC and Department to manage uncertainty associated with this submission, whilst considering risk sharing arrangements (RSAs) already negotiated. The pre-PBAC response proposed revised increases to the annual caps for CDKIs as shown in Table 23, based on revised durations of therapy for RIBO+FULV in the first and second-line settings which reduced the weighted price for ribociclib (versus the price proposed in the submission).
- 6.92 The increases to the financial caps proposed in the pre-PBAC response would result in a net cost to PBS/RPBS of \$100 million to < \$200 million over the first 6 years of listing. There is likely to be significant overlap between the proposed and existing populations and any offsets for reduced use of CDKIs under the existing listing would need to be adequately accounted for in RSAs.

Table 23: Pre-PBAC response proposed increase to the RSA caps for CDKIs

Net impact to the PBS	2021	2022	2023	2024	2025	2026
RIBO net impact – Population 1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
RIBO cost to govt.- Population 2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
RIBO cost to govt. - Population 3	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
RIBO cost to govt. - Population 4	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

*Based on a confidential weighted effective AEMP of \$ [REDACTED] revised as per DUSC recommendations for first and second line treatment durations.

- 6.93 The PBAC noted that the revised financial caps were not evaluated as they were provided in the pre-PBAC response. The PBAC considered it was unclear why there was a proposed increase to the CDKI caps for population 1 given this population was intended to represent first-line patients substituting CDKI+NSAI.
- 6.94 In its March 2018 recommendation of ribociclib, the PBAC considered that cost-effectiveness (in that setting) could be improved “via a reduction in price in conjunction with financial caps” (Para 6.1, ribociclib PSD, March 2019). The PBAC noted that caps were intended to be exceeded by 27% to achieve cost-effective net pricing.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation to extend the listing of ribociclib to include use in combination with fulvestrant for the treatment of patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) unresectable advanced or metastatic breast cancer. The PBAC recognised the clinical need for this combination therapy. The PBAC was of a mind to recommend ribociclib in combination with fulvestrant (RIBO+FULV), but considered that there remains a need to resolve the appropriate weighted price, financial impact and changes to risk sharing arrangements for ribociclib.
- 7.2 The PBAC was satisfied that RIBO+FULV is non-inferior to RIBO+NSAI in terms of PFS. The PBAC was satisfied that RIBO+FULV provides, for some patients, a significant improvement in PFS and a reduction in toxicity over EVE+EXE.
- 7.3 The PBAC agreed with comments from BCNA and MOGA breast cancer expert group that the main clinical need for RIBO+FULV combination therapy was:
- In the first-line setting: patients who relapse on or within 12 months of prior (neo)adjuvant treatment with an AI for early breast cancer (NSAI-resistant).
 - In the subsequent-line setting: for patients who received single-agent NSAI first-line before the CDKIs were available. The PBAC also considered that there may be a small group of patients who are elderly or who have poor performance status, in whom single-agent NSAIs may be used first-line, but who are then considered suitable for CDKI combination therapy in the second-line setting.
- 7.4 The PBAC noted that the consumer comments also reflected these areas of high clinical need. The PBAC considered that the majority of use in the longer term is likely to be in the first-line setting, as use of CDKIs as initial treatment is the standard of care for most patients. The PBAC considered that use of RIBO+FULV was likely to be the preferred approach in patients who relapsed on NSAI in the adjuvant setting. The PBAC considered that there would be relatively few patients eligible for treatment under the subsequent-line listing and this number is likely to be declining, though the clinical need for access to ribociclib for these patients is high.

- 7.5 The submission proposed amending the existing listings for ribociclib (initial and continuing) by: (1) allowing use in combination with fulvestrant (or, per the existing listing, with anastrozole or letrozole); and (2) adding new second-line treatment listings for ribociclib. New grandfather listings were also requested for both lines of treatment.
- 7.6 The submission nominated RIBO+NSAI as the main comparator for the first-line setting, and EVE+EXE for the second-line setting. The PBAC considered that the nominated comparator in the first-line setting was appropriate. The PBAC considered that, in the second-line setting, a mix of other treatments such as chemotherapy (e.g. capecitabine) and endocrine therapies (e.g. tamoxifen or fulvestrant monotherapy) could also be considered comparators for some patients.
- 7.7 The clinical evidence was based on three main trials, which were the basis of the unanchored MAICs presented. MONALEESA-3, MONLEESA-2 and BOLERO-2 were all randomized double-blind studies. The PBAC noted that unanchored MAICs can be more prone to uncertainty than anchored MAICs and considered that the risk of bias due to the indirect nature of the comparisons was high.
- 7.8 For the first-line treatment setting, the submission presented an unanchored MAIC between the RIBO+FULV arm of MONALEESA-3 (subgroup of patients with no prior treatment in the advanced/metastatic setting excluding those who were resistant to (neo)adjuvant NSAI) and the RIBO+NSAI arm of MONALEESA-2. The PBAC considered that the baseline characteristics of MONALEESA-2 and the included subgroup of MONALEESA-3 were reasonably well balanced even before weighting. The PBAC considered that the covariates included in the analysis (including prior chemotherapy) appeared reasonable. The PBAC agreed with the ESC that the unanchored MAIC for the endpoint of PFS was likely to be valid for the claim of non-inferiority to RIBO+NSAI in the first-line setting.
- 7.9 For the first-line analysis, the PBAC noted that the PFS HR was 0.92 (0.72, 1.18) and the upper confidence interval was below the non-inferiority margin of 1.4 accepted in PBAC considerations of palbociclib (March 2018 PBAC meeting) and abemaciclib (March 2019 PBAC meeting). However, the PBAC considered that the OS data from MONALEESA-2 were immature and the confidence intervals from the unanchored MAIC were wide (HR for OS: 1.08 (95% CI: 0.73, 1.60)) but improved slightly when prior chemotherapy was included as a covariate (HR for OS: 1.03 (95% CI: 0.69, 1.52)). The PBAC noted that recommendations for palbociclib and abemaciclib were based on non-inferior PFS and considered that the claim of non-inferior comparative effectiveness in the first line setting based on the outcome of PFS was reasonable.
- 7.10 The PBAC considered that the claim of non-inferior comparative safety versus RIBO+NSAI in the first line setting was reasonable. However, the PBAC noted that the MONALEESA-3 trial indicated that combination therapy with RIBO+FULV had substantively inferior safety to fulvestrant alone.

- 7.11 For the second-line treatment setting, the submission presented an unanchored MAIC between the subgroup of second-line patients in the RIBO+FULV arm of MONALEESA-3 and the subgroup of second-line patients in the EVE+EXE arm of BOLERO-2. The reliance on subgroups substantially reduced the size of the population available for analysis. The PBAC considered there were significant imbalances between the baseline characteristics of the MONALEESA-3 and BOLERO 2 subgroups (e.g. in terms of age, proportion of patients with visceral disease and number of metastatic sites involved). While weighting may have corrected for these factors, the PBAC considered these imbalances indicated differences in the patient populations, increasing the likelihood of bias due to unobserved confounders. Notwithstanding these limitations, the PBAC considered that it appeared that the subgroups included in the unanchored MAIC were sufficiently balanced for the comparison to be informative. The PBAC noted the results of the unanchored MAIC for RIBO+FULV compared with EVE+EXE in the second-line setting were: HR for PFS of 0.40 (95%CI: 0.27, 0.56) and HR for OS of 0.56 (95%CI: 0.38, 0.80). The PBAC considered that the true uncertainty in the PFS and OS hazard ratios is likely to be much greater than reported.
- 7.12 The PBAC considered that the claim of superior comparative effectiveness in the second-line treatment setting was supported, however, the magnitude of benefit for RIBO+FULV over EVE+EXE was highly uncertain given the potential for bias in the unanchored MAIC. Given the significant limitations of the clinical data, in accepting this claim, the PBAC took into account the high clinical need in a very small patient population.
- 7.13 The PBAC considered that the claim of superior comparative safety was based on limited clinical data but appeared clinically reasonable.
- 7.14 For the first-line setting, the PBAC considered that a cost-minimisation analysis was reasonable, given the clinical claim of non-inferior effectiveness and safety was accepted for RIBO+FULV compared with RIBO+NSAI. The PBAC noted that the cost-minimisation of RIBO+FULV was dependent on availability of generic fulvestrant at the price proposed in the submission. The PBAC considered that the comparator price for currently listed ribociclib (in combination with NSAIs) applied in the cost-minimisation analysis should take into account the effective price that was intended for RIBO+NSAI including both the effective price and the intended RSA rebate for breaching the subsidisation caps, given the cost-effective net cost of ribociclib (in that setting) was intended to be achieved through both the AEMP and rebates achieved through the financial caps.
- 7.15 The PBAC considered that the structure of the economic model for the second line comparison with EVE+EXE was reasonable. However, the PBAC noted that the economic model relied on hazard ratios from the unanchored MAIC, which it considered had a high level of inherent uncertainty resulting in an uncertain magnitude of benefit for RIBO+FULV compared with EVE+EXE as discussed above. The PBAC noted that the ICER was sensitive to the hazard ratios applied to estimate PFS and OS for EVE+EXE and therefore the ICERs generated were uncertain and may be

underestimated.

- 7.16 The PBAC considered that the extrapolation of the highly uncertain data from the unanchored MAIC to 10 years substantially increased the uncertainty of the cost-effectiveness estimates. The PBAC considered that greater confidence would be derived by limiting the time horizon to a shorter duration, more in line with that previously accepted for RIBO+NSAI. The PBAC noted that RIBO+NSAI was recommended on the basis of a model with a 7 year time horizon, reflecting uncertainty in the long term survival outcomes for RIBO+NSAI.
- 7.17 The PBAC noted that PFS and OS for RIBO+FULV were extrapolated using exponential functions, and no observed trial data were applied in the model. PFS and OS for EVE+EXE were estimated by applying hazard ratios from the unanchored MAIC to PFS and OS in the RIBO+FULV arm. The PBAC considered that the extrapolation appeared to be a poor visual fit to the observed data, and appeared to underestimate the OS for EVE+EXE in the first 3 years of the model. The PBAC considered that the model should use observed KM data up to the time point at which the observed data becomes unreliable as a result of small numbers of patients remaining event-free. Extrapolations applied beyond this point should be informed by all available data. The PBAC considered that the methodology used by the evaluation to correct for this (which resulted in an ICER of \$55,000 to < \$75,000/QALY) was appropriate.
- 7.18 The PBAC considered that the economic model in the second-line setting should use Kaplan-Meier data up to the point of median follow-up (using the evaluation's methodology), and use a time horizon of 7 years. The PBAC considered that with the model respecified in this way, the second-line price for RIBO+FULV should be reduced so that the ICER is below \$55,000 to < \$75,000 per QALY. The PBAC considered this ICER would be acceptable in the context of a small and decreasing second line population.
- 7.19 The submission estimated the number of patients in first and second line using a mixed market share and epidemiological approach, dividing patients into four populations. The PBAC considered that many of the assumptions used were uncertain and likely substantially overestimated the number of treated patients because:
- Population 1 (first-line, patients substituting RIBO+FULV for CDKI+NSAI) was overestimated as the PBAC considered that it was unlikely that patients would prefer a parenteral treatment (fulvestrant) over an oral NSAI. The PBAC also considered that the rates of growth of the market for this population appear to be overestimated and are likely to stabilise as CDKIs have been subsidised on the PBS since July 2018.
 - Population 2 (first-line, growth of CDKI market from patients substituting for chemotherapy or AI monotherapy). The PBAC considered that uptake in this population is likely to be very small as patients currently receiving chemotherapy would largely be intolerant to or unsuitable for treatment with a CDKI, and only a

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- very small proportion of patients currently receiving AI monotherapy would be suitable for second-line treatment with a CDKI.
- Population 3 (second-line, patients displacing EVE+EXE). The PBAC considered that this population appeared to be overestimated as growth in everolimus was assumed to be stable over the forward estimates, whereas DUSC noted that its use is declining.
 - Population 4 (second-line, patients displacing EXE only). The PBAC considered that the estimated 50% of patients not fit for CDKI in the first line setting who are subsequently eligible for these agents in the second line setting was substantially overestimated and this population was likely to be very small.
- 7.20 The PBAC noted that the group of prevalent patients who began treatment with AI monotherapy prior to listing of RIBO+NSAI would be included in populations 3 and 4. The PBAC considered that this would be the key use of RIBO+FULV in the second-line setting, but that this would be a relatively small and declining population. Overall, the PBAC considered that the relative use of RIBO+FULV in the second and subsequent-line setting would be substantially smaller than in the first-line setting.
- 7.21 The PBAC agreed with DUSC that cost offsets from EVE+EXE were overestimated as these treatments are likely to be displaced to a later line of therapy rather than replaced by RIBO+FULV.
- 7.22 The PBAC noted that the price proposed for first-line treatment was lower than the current price for ribociclib (due to the higher price for fulvestrant compared with NSAI) and the submission proposed a significantly higher price for ribociclib in subsequent-line therapy based on the claim of superior efficacy to EVE+EXE. The weighted effective AEMP proposed in the submission was \$ [REDACTED] for the 600 mg dose (63 tablets per pack). The relative use of ribociclib in the first-line and subsequent line settings impacted on the weighted effective price and use in each setting was dependent on both the assumed patient split and the treatment duration in each setting. After applying DUSC's estimates of mean prescription duration of 20.2 months for first line and 13.3 months for subsequent lines, the weighted effective AEMP for ribociclib proposed in the pre-PBAC response was reduced to \$ [REDACTED]. The PBAC noted that this was based on the assumption that [REDACTED]% of use would be in the first-line setting, which the PBAC considered was uncertain and likely underestimated.
- 7.23 The pre-PBAC response requested an increase in the financial caps of \$100 million to < \$200 million over the first 6 years of listing. The PBAC considered that the submission had substantially overestimated the likely increase in use of CDKIs that would occur with the listing of RIBO+FULV, and that the total increase in the CDKI market as a result of listing RIBO+FULV would be very small (as outlined in Paragraphs 7.3 and 7.4). Overall, the PBAC considered that only a small increase in financial caps would be justifiable.
- 7.24 The PBAC noted that the existing CDKI caps were intended to be exceeded by 27% in order to achieve cost-effective net cost as per the RIBO+NSAI submission. The PBAC

noted that these caps are not currently being reached and therefore the cost-effectiveness of ribociclib (and other CDKIs) in the current listing is uncertain. Given the highly uncertain patient numbers for the proposed new listing, the PBAC considered that the AEMP in the first-line setting (which was cost-minimised against RIBO+NSAI) should be based on the intended cost-effective price for the existing listing of ribociclib (i.e. the effective net cost that was intended for ribociclib including both the effective price and the intended RSA rebate for breaching the subsidisation caps).

- 7.25 The PBAC considered that the sponsor should provide the following further information:
- revise the economic model in the second-line setting as outlined in paragraph 7.18.
 - revise the financial estimates, weighted price and proposed increase to the RSA caps as outlined above.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

Novartis are committed to working with the PBAC to achieve sustainable PBS listing conditions and timely patient access to Kisqali® (ribociclib) in combination with fulvestrant.