

**7.13 RIBOCICLIB,
200 mg tablet, 21, 42, 63
Kisqali,
Novartis Pharmaceuticals Australia Pty Ltd**

1 Purpose of Application

- 1.1 At its July 2020 meeting the PBAC considered a major submission seeking a Section 85 Authority Required PBS listing for ribociclib (200 mg tablets) to be used in combination with fulvestrant (250mg/5mL injection) for the treatment of patients with hormone receptor positive (HR+), human epidermal growth factor receptor-2 negative (HER2-) advanced or metastatic breast cancer. The PBAC deferred making a recommendation at the July 2020 meeting. The minor resubmission sought to amend the economic model and resolve the outstanding matters as requested by the PBAC including a reduced weighted price and reduced financial estimates.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus ribociclib plus non-steroidal aromatase inhibitors (RIBO+NSAI) in first-line treatment and a cost-effectiveness analysis versus everolimus plus exemestane (EVE+EXE) in subsequent-line treatment.

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 July 2020 submission

2 Background

Registration status

- 2.1 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”.
- 2.2 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).
- 2.3 As noted above, the TGA indication for ribociclib includes combination use with fulvestrant. Consequently, combination use (in first or second-line) is considered to be “on-label”.

Previous PBAC consideration

- 2.4 Fulvestrant (as combination therapy or as monotherapy) is not currently PBS listed for any indication. At its July 2020 meeting the PBAC recommended listing of fulvestrant for the treatment of patients with HR+, HER2- unresectable advanced or metastatic breast cancer.

Public Summary Document – November 2020 PBAC Meeting

- 2.5 Ribociclib as combination treatment with an NSAI, was recommended for the treatment of patients with HR+, HER2- unresectable advanced or metastatic breast cancer at the March 2018 PBAC meeting.
- 2.6 At its July 2020 meeting the PBAC deferred making a recommendation to extend the listing of ribociclib to include combination use with fulvestrant. The PBAC was of a mind to recommend ribociclib in combination with fulvestrant (RIBO+FULV), but considered there was a need to resolve the appropriate weighted price, financial impact and changes to risk sharing arrangements for ribociclib (paragraph 7.1, ribociclib, Public Summary Document (PSD), July 2020 PBAC Meeting). The PBAC also advised that revisions to the economic model were required and the second-line price for RIBO+FULV should be reduced so that the ICER is below \$55,000 to < \$75,000 per QALY (paragraph 7.18, ribociclib PSD, July 2020 PBAC Meeting).
- 2.7 A summary of the previous submission/s and current submission is provided in the table below.

Public Summary Document – November 2020 PBAC Meeting

Table 2: Summary of the previous submissions and current resubmission

	July 2020 submission	Current resubmission
Requested PBS listing	Treatment of non-premenopausal patients with HR+/-HER2- locally advanced or metastatic breast cancer, in combination with fulvestrant (in first or subsequent lines).	Unchanged
Requested effective AEMPs Ribociclib	600 mg dose (200 mg, 63 tablets per pack) 1L AEMP: \$ [REDACTED] 2L AEMP: \$ [REDACTED] Weighted AEMP: \$ [REDACTED] (63% 1L) Weighted AEMP, pre-PBAC response: \$ [REDACTED] (71.5% 1L)	600 mg dose (200 mg, 63 tablets per pack) 1L AEMP: \$ [REDACTED] (unchanged) 2L AEMP: \$ [REDACTED] (reduced) Weighted AEMP using this approach would be \$ [REDACTED] (76% 1L overall, 49% in yr 1 and up to 87% in yr 6), though the resubmission proposed a further reduction with a weighted AEMP of \$ [REDACTED], consistent with the current ribociclib price in its existing listing.
Requested effective AEMP Fulvestrant	\$ [REDACTED]	Unchanged
Comparator	1L: RIBO+NSAI 2L: EXE+EVE	Unchanged
Clinical evidence	MONALEESA-3 (RIBO+FULV vs PBO+FULV) 1L: unanchored MAIC using MONALEESA-2 (RIBO+NSAI vs PBO+FULV) 2L: unanchored MAIC using BOLERO-2 (EVE+EXE vs PBO+EXE)	Unchanged
Key effectiveness data	1L Weighted PFS HR 0.92 (95% CI: 0.72, 1.18) Absolute difference median PFS 2.5 months (95% CI: -3.9, 10.9) Weighted OS HR 1.08 (95% CI: 0.73, 1.60) Median OS not reached for active arms 2L Weighted PFS HR 0.40 (95% CI: 0.27, 0.56) Absolute difference median PFS 11.0 months (95% CI: 4.5, 16.0; p<0.0001) Weighted OS HR 0.56 (95% CI: 0.38, 0.80; p=0.004) Median OS not reached for RIBO+FULV	Unchanged
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.	Unchanged
Economic evaluation	1L Cost-minimisation vs RIBO+NSAI assuming no difference in dose, duration or dose intensity. 2L Cost-effectiveness analysis vs EVE+EXE	1L Cost-minimisation unchanged 2L Cost-effectiveness analysis including changes: <ul style="list-style-type: none"> • reduction in time horizon from 10 years to 7 years • extrapolation of survival curves methodology changed

Public Summary Document – November 2020 PBAC Meeting

	July 2020 submission	Current resubmission
Number of patients	The submission used a combined epidemiological and market share approach. 1L: Estimated 500 to < 5000 patients (500 to < 5,000 scripts) in year 1, increasing to 500 to < 5,000 patients (20,000 to < 30,000 scripts) in year 6. 2L: Estimated 500 to < 5000 patients (5,000 to < 10,000 scripts) in year 1, increasing to 627 patients (10,000 to < 20,000 scripts) in year 6. (paragraph 6.79, Table 22)	Overall approach unchanged. Changes include: <ul style="list-style-type: none"> • reduced uptake and substitution rates • assumed EVE+EXE negative growth • price reduced 1L: Estimated < 500 patients (5,000 to < 10,000) in year 1, increasing to 500 to < 5,000 patients (20,000 to < 30,000 scripts) in year 6. 2L: Estimated < 500 patients (5,000 to < 10,000 scripts) in year 1, decreasing to < 500 patients (500 to < 5,000 scripts) in year 6.
Estimated net cost to PBS	Net cost to PBS/RPBS of \$50 million to < \$60 million in Year 6, and a total of \$200 million to < \$300 million in the first 6 years of listing.	Net cost to PBS/RPBS of \$10 million to < \$20 million in Year 6, and a total of \$80 million to < \$90 million in the first 6 years of listing.
Risk sharing arrangement	The increases to the financial caps proposed in the pre-PBAC response would result in a net cost to PBS/RPBS of \$90 million to < \$100 million over the first 5 years of listing. (paragraph 6.92)	Net cost to PBS/RPBS of \$40 million to < \$50 million over the first 5 years of listing (\$30 million to < \$40 million for 2L). Existing 1L caps: \$200 million to < \$300 million over 5 years.
PBAC decision	Defer PBAC Comment: 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. (paragraph 7.1)	-

Source: Paragraph references refer to the RIBO+FULV July 2020 PSD.

For more detail on PBAC’s view, see section 5 PBAC outcome.

3 Requested listing

3.1 The requested listing for ribociclib, proposed by the sponsor, is unchanged from the previous submission and is reproduced below.

Public Summary Document – November 2020 PBAC Meeting

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: \$5,536.97 ^b	Kisqali, Novartis Pharmaceuticals Australia Pty Limited
		42 ^a		EP: \$ [REDACTED]	
		21 ^a		PP: \$3,750.30 ^b	
				EP: \$ [REDACTED]	
				PP: \$1,956.46 ^b	
				EP: \$ [REDACTED]	

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) = 1x 21 days.

^b Published price. Special pricing arrangements apply for the effective prices. Approved ex-manufacturer price for ribociclib 600mg is \$ [REDACTED].

Amend existing listing/s as follows (changes to existing first-line listing are shown in italics):

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 endocrine therapy 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 <i>or 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 <i>or 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

Public Summary Document – November 2020 PBAC Meeting

Add new indications to ribociclib as follows:

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

Public Summary Document – November 2020 PBAC Meeting

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 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

- 3.2 The July 2020 submission requested a higher price for the proposed new listing of ribociclib (i.e. for use in combination with fulvestrant) than currently applies to the existing listing (which is for use in combination with a non-steroidal aromatase inhibitor (NSAI; letrozole or anastrozole)). The resubmission requested the same effective AEMP (and Special Pricing Arrangement) as applies to the existing listing.
- 3.3 The PBAC previously considered that the listing for fulvestrant (for use in combination with ribociclib) should combine initial and continuing treatment (paragraph 3.3 ribociclib PSD, July 2020 PBAC meeting).
- 3.4 The PBAC recalled its July 2020 consideration of a submission for fulvestrant monotherapy and noted that fulvestrant would be acceptably cost-effective for use as monotherapy at the price proposed in this submission. Thus, the PBAC reiterated its July 2020 recommendation for a broad listing for fulvestrant that allows use as monotherapy and reiterated its recommended listing for fulvestrant from July 2020, which is outlined in Section 6 ‘Recommended listing’. The PBAC noted that this restriction would also allow use of fulvestrant in combination with ribociclib due to the proposed changes to the ribociclib listing.
- 3.5 The PBAC considered it would be preferable to simplify the initial ribociclib restrictions to have a single initial restriction combining first and subsequent line treatment in order to help avoid confusion as to what constitutes the various ‘lines’ of therapy. For example, the previous Public Summary Document (PSD) noted that, consistent with the existing restrictions for CDKIs+NSAIs, the proposed criterion excluding patients

who received prior endocrine therapy in the ‘first-line’ setting would still permit patients with visceral disease who received chemotherapy before endocrine therapy to access RIBO+FULV. The PBAC noted that a combined listing would result in ribociclib having a significantly different restriction to the other CDKIs, but considered this would be reasonable. The PBAC also considered restrictions combining first and subsequent line treatment would be appropriate for grandfather and continuing restrictions.

For more detail on PBAC’s view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

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

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (1), and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the benefits of an oral medication (ribociclib), with increased flexibility in hospital attendance for administration and improved side-effect profile compared with chemotherapy.

4.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the ribociclib + fulvestrant submission, 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 in combination with fulvestrant, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹ based on a comparison of PFS with placebo, as median OS of the RIBO+FULV arm in the MONALEESA-3 trial had not yet been reached. MOGA noted that the score is likely to increase to 4 once median OS is reached.

Clinical evidence

4.4 In July 2020, the PBAC considered:

- the claim of non-inferior comparative effectiveness in the first line setting based on the outcome of PFS was reasonable (paragraph 7.9 ribociclib PSD, July 2020 PBAC meeting);
- the claim of non-inferior comparative safety versus RIBO+NSAI in the first line setting was reasonable (paragraph 7.10, ribociclib PSD, July 2020 PBAC meeting);

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

- 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 (paragraph 7.12, ribociclib PSD, July 2020 PBAC meeting); and
- the claim of superior comparative safety versus EVE+EXE was based on limited clinical data but appeared clinically reasonable (paragraph 7.13, ribociclib PSD, July 2020 PBAC meeting).

4.5 The PBAC noted that no additional clinical data were presented in the minor resubmission and its consideration of the clinical claims were unchanged from the July 2020 submission as outlined above.

Economic analysis

First line

4.6 The submission considered by the PBAC in July 2020 presented a cost minimisation analysis of RIBO+FULV versus RIBO+NSAI as first line treatment. The PBAC previously considered this was appropriate. The minor resubmission did not propose any changes to the cost-minimisation analysis, or the price of ribociclib derived from this approach.

4.7 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.

4.8 The results of the cost-minimisation analysis are presented in the table below.

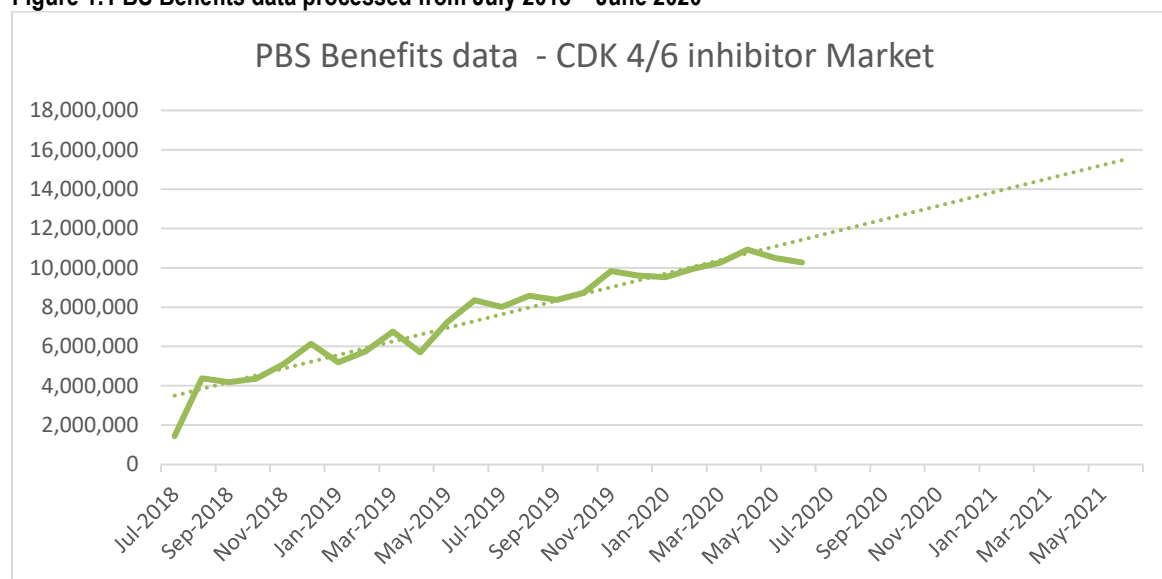
Table 3: Results of the cost-minimisation analysis

Component	RIBO+FULV	RIBO+NSAI	Difference
Step 1: Treatment costs if ribociclib price were the same as the existing listing			
Medicine costs (28-day cycle)			
Ribociclib, AEMP (at current price)	\$ [REDACTED]	\$ [REDACTED]	\$0.00
• With relative dose intensity (85.2%)	\$ [REDACTED]	\$ [REDACTED]	\$0.00
Fulvestrant, AEMP	\$ [REDACTED]	\$0.00	\$ [REDACTED]
Fulvestrant loading dose, AEMP	\$ [REDACTED]	\$0.00	\$ [REDACTED]
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 28-day cycle	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Step 2: Price of ribociclib required for cost-minimisation (no net difference in total cost per cycle)			
Ribociclib, AEMP (proposed)	\$ [REDACTED]		

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.

- 4.9 If the ribociclib price were the same as in the existing listing, the treatment cost of RIBO+FULV would be \$ [REDACTED] higher than RIBO+NSAI (per 28-day cycle) due to fulvestrant having a higher price than the NSAIs. Thus, a lower price is required for ribociclib when used in combination with fulvestrant than the current price in combination with an NSAI. As such, the proposed effective AEMP for ribociclib 600 mg dose in this setting was \$ [REDACTED], which is 22% lower than the ribociclib price in the RIBO+NSAI combination.
- 4.10 The cost-minimisation analysis was based on the current AEMP of ribociclib (in its current listing for use in combination with NSAI). In July 2020, the PBAC noted that, at the time of recommending ribociclib for use in combination with an NSAI, the CDKI caps were intended to be exceeded by 27% in order to achieve a 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) (paragraph 7.24, ribociclib PSD, July 2020 PBAC meeting). The PBAC noted that the most recent data, up to the end of year 2 of the caps, indicate that the current CDKI caps reached 95.5% in year 2 and the resubmission stated that it is expected that the caps will be exceeded in years 3-5.
- 4.11 The resubmission noted that during negotiations, the AEMP was reduced thus reducing the proportion by which the caps were intended to be exceeded from 27% to 21.9%. The resubmission maintained the previously proposed ribociclib AEMP of \$ [REDACTED] for the following reasons:
- The resubmission stated that the reduction in the effective price and the RSA for the RIBO+NSAI submission was to address concerns around the immature OS for the MONALEESA-2 data. The resubmission noted that, since this time, statistically significant overall survival gain has been reported for pre-menopausal patients in the pivotal MONALEESA-7 study. The resubmission also argued that this is not the case with the current submission, which is based on the MONALEESA-3 data wherein the secondary endpoint of OS was met.
 - The resubmission noted that although caps were not reached in the first two years of listing the financial caps are expected to be breached in years 3, 4 and 5 due to increased utilisation due to market growth from listing of palbociclib and abemaciclib.
- 4.12 The resubmission presented the following figure showing the increase in the CDK 4/6 inhibitor market.

Figure 1: PBS Benefits data processed from July 2018 – June 2020



Source: Figure 1, p5 of the resubmission.

4.13 The PBAC noted that the requested ribociclib price is not consistent with the intended cost-effective price for the existing listing of ribociclib when the cost of concomitant therapies are taken into account. However, the PBAC noted that the requested price of ribociclib is 22% lower than in the existing listing. Thus, based on the ribociclib component alone (i.e. without taking into account the cost of fulvestrant or an NSAID), the proposed AEMP in the first-line setting is consistent with 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).

Second/subsequent line

4.14 The July 2020 submission also presented a cost-effectiveness analysis for RIBO+FULV versus EVE+EXE in second/subsequent line treatment. The PBAC requested two changes to this model: a 7-year time horizon; and adjustment to the methodology for extrapolation of survival data. The PBAC also advised that the price should be reduced in order to achieve an ICER of <\$55,000 to < \$75,000 per QALY in this setting. This was in the context of the uncertainty that is associated with an unanchored MAIC.

4.15 The resubmission accepted the 7-year time horizon in the context of the uncertain comparative data.

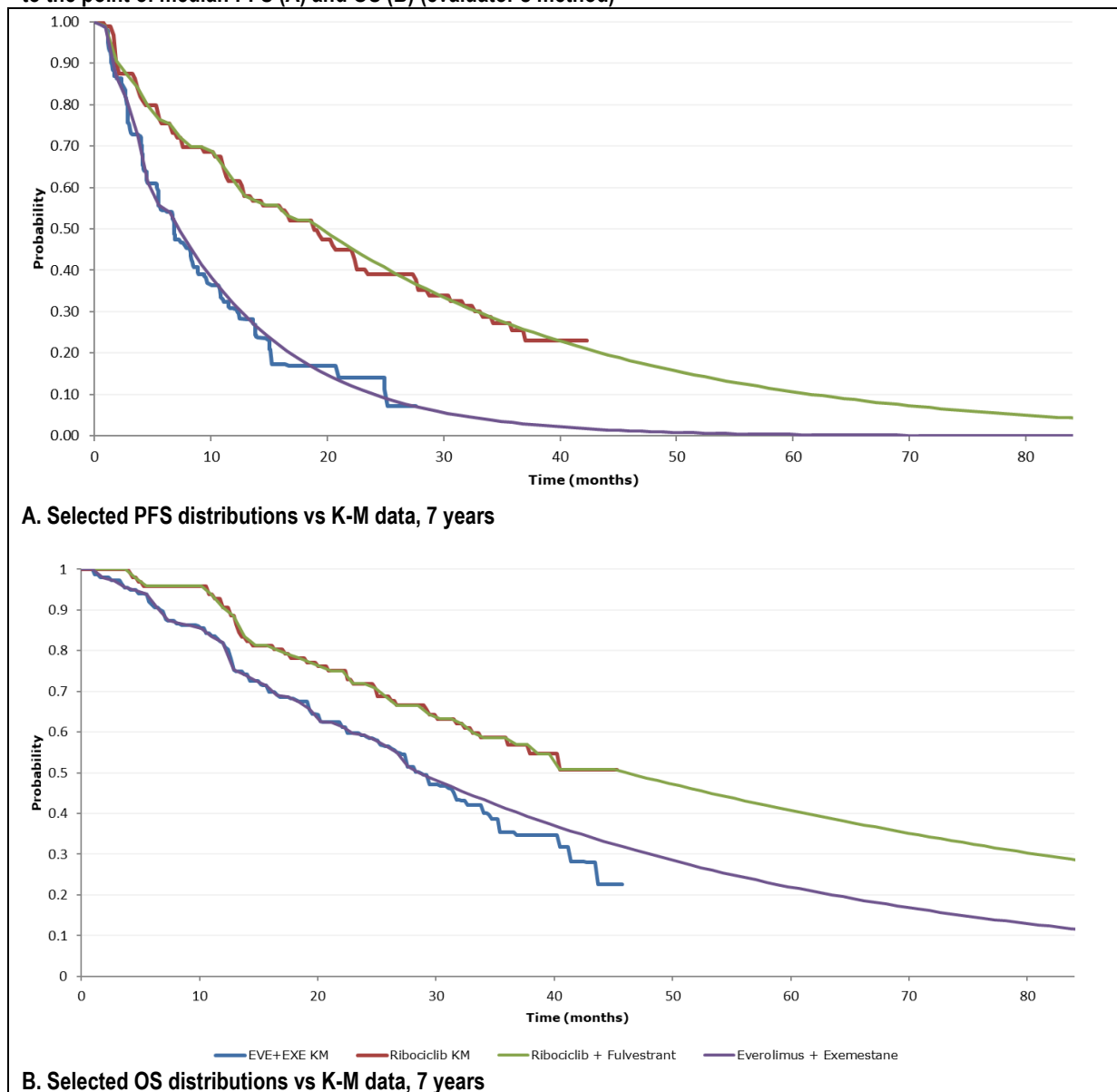
4.16 In its consideration of the July 2020 submission, the PBAC noted that “PFS and OS for RIBO+FULV were extrapolated using exponential functions, and no observed trial data were applied in the model. PFS and OS for EVE+EXE were estimated by applying hazard ratios from the unanchored MAIC to PFS and OS in the RIBO+FULV arm. The PBAC considered that the extrapolation appeared to be a poor visual fit to the observed

Public Summary Document – November 2020 PBAC Meeting

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.” (paragraph 7.17, ribociclib PSD, July 2020 PBAC meeting). The evaluator’s revised extrapolations are shown in Figure 2.

- 4.17 The minor resubmission noted that the evaluator’s approach used Kaplan-Meier (K-M) data up to the point of median survival, whereas the PBAC recommended use of K-M data up to the point of median follow-up.

Figure 2: Observed and modelled PFS and OS for patients treated with RIBO+FULV and EVE+EXE using K-M data up to the point of median PFS (A) and OS (B) (evaluator’s method)



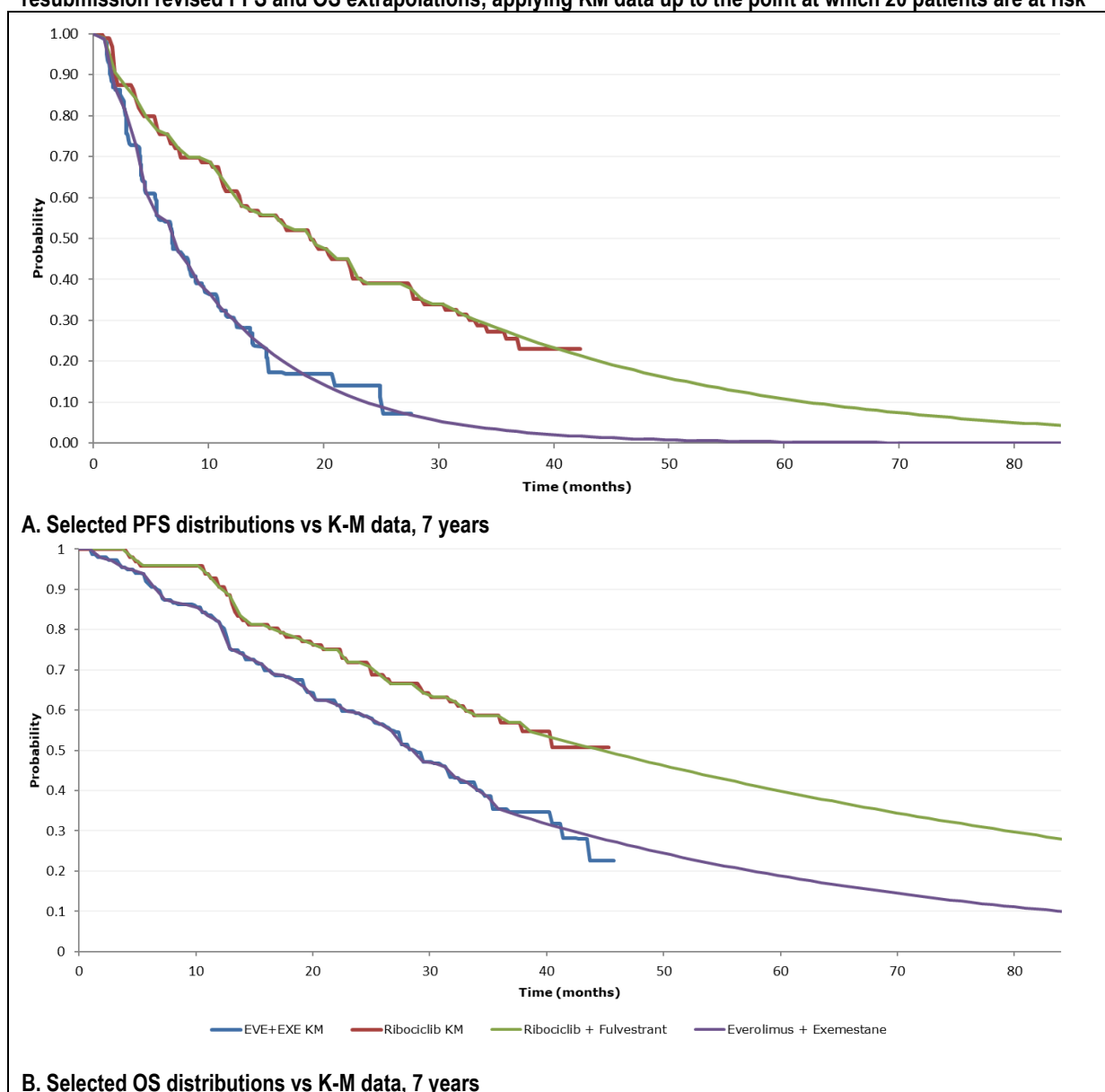
Source: Constructed for the minor overview using the resubmission CEA model, worksheet “Efficacy PFS” and “Efficacy PPS_OS”.
 Note: the evaluator’s method uses the K-M data up to median survival. As median OS was not reached in the relevant MONALEESA-3 subgroup, almost all the K-M data were used in the extrapolation of OS in the RIBO+FULV arm.

4.18 The minor resubmission did not agree with the evaluator’s methodology for extrapolation of the K-M data. The resubmission noted that truncation of the observed data at the median survival estimates (as per the evaluators approach) lead to inconsistent numbers of patients at risk across the arms (as shown in the table below), and lead to use of all the observed K-M data in the extrapolation of OS in the RIBO+FULV arm. The resubmission also argued that statistical literature suggests only around 10-20% of patients are required to be at risk of an event for K-M curves to remain reliable. On this basis the resubmission proposed, with a sample size of 100,

approximately 20 patients at risk would be a more appropriate threshold at which the observed data becomes less reliable.

4.19 As such, the sponsor proposed an alternative approach to PFS and OS extrapolations using the evaluator’s extrapolation approach but using K-M data up to the point where 20 patients remained at risk. Figure 3 shows the resubmission’s amended PFS and OS extrapolations.

Figure 3: Observed and modelled PFS (A) and OS (B) for patients treated with RIBO+FULV and EVE+EXE - resubmission revised PFS and OS extrapolations, applying KM data up to the point at which 20 patients are at risk



Source: Constructed for the minor overview using the resubmission CEA model, worksheet “Efficacy PFS” and “Efficacy PPS_OS”.

4.20 The PBAC noted that the PBAC Guidelines (version 5, Section 3A.4.3) state “Where extrapolation is undertaken, use observed time-to-event data in preference to

Public Summary Document – November 2020 PBAC Meeting

modelled data up to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free”.

- 4.21 The PBAC noted that extrapolating from the point of median follow-up (39 months for RIBO+FULV and 18 months for EVE+EXE) resulted in a slight increase in the ICER. The PBAC noted that this approach used more PFS K-M data for the EVE+EXE arm, but less OS K-M data for the EVE+EXE arm than the resubmission’s approach and that this approach may overestimate OS for the EVE+EXE arm. Overall, the PBAC considered that the resubmission’s approach to extrapolation appeared reasonable and resulted in survival curves that had good visual fit to the observed data. Further the PBAC considered that the resubmission’s approach was consistent with the recommendation in the guidelines to use observed time-to-event data in preference to modelled data up to the time point at which the observed data become unreliable as a result of small numbers of patients remaining event-free.
- 4.22 The resubmission recalculated ICERs using K-M data up to the point where 20 patients remained at risk, along with sensitivity analyses using 25 patients and 15 patients as shown in Table 4. These revised ICERs were not independently evaluated as this was a minor resubmission.

Table 4: Months of PFS and OS where KM data is reliable

Point to which K-M data used	RIBO+FULV, n = 100		EVE+EXE, n = 101		ICER/QALY (10- or 7- year horizon) AEMP: \$ [redacted]	Calculated AEMP for ICER <\$55,000 to < \$75,000, 7-year horizon [^]
	PFS months	OS months	PFS months	OS months		
20% of patients at risk, n = 20	33	39	12	36	10: \$ [redacted] ¹ 7: \$ [redacted] ¹	\$ [redacted] (-10.0%)
Alternative methods						
Median survival (n patients at risk)	19.3 (~41 at risk)	45.3 (<5 at risk)	6.9 (~37 at risk)	29.4 (42 at risk)	10: \$ [redacted] ^{*1} 7: \$ [redacted] ^{#1}	\$ [redacted] (-15.7%)
Median follow-up	39	39	18	18	10: \$ [redacted] ¹ 7: \$ [redacted] ¹	\$ [redacted] (-17.3%)
Sensitivity analyses +/- 5%						
25% of patients at risk, n = 25	31	38	10	35	10: \$ [redacted] ¹ 7: \$ [redacted] ¹	\$ [redacted] (-9.8%)
15% of patients at risk, n = 15	35	40	13	37.5	10: \$ [redacted] ¹ 7: \$ [redacted] ¹	\$ [redacted] (-9.9%)

Source: Table 3, p. 8 of the resubmission; **Bold** indicates price proposed by the sponsor

* evaluation methodology updated with Aug 2020 prices, this becomes \$ [redacted]¹, # updated with Aug 2020 prices, this becomes \$ [redacted]¹,

[^] Brackets indicate reduction in AEMP required, compared with the 2L price in the July 2020 submission (AEMP: \$ [redacted]).

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

- 4.23 The resubmission proposed an AEMP of \$ [redacted] (in this setting) based on a revised base case comprising a 7 year time horizon, and observed K-M data up to the point at which 20% of patients remain at risk, with an ICER of \$55,000 to < \$75,000/QALY.

Drug cost/patient/course

- 4.24 The estimated drug cost/patient/course for RIBO+FULV in first line treatment would be \$ [REDACTED] (\$ [REDACTED] for ribociclib, and \$ [REDACTED] for the fulvestrant component, based on a course duration of 20.2 months (21.96 cycles, per the financial estimates) and weighted DPMQ of \$ [REDACTED] for ribociclib and DPMA \$ [REDACTED] for fulvestrant.
- 4.25 The estimated drug cost/patient/course for RIBO+FULV in second line treatment would be \$ [REDACTED] (\$ [REDACTED] for ribociclib, and \$ [REDACTED] for the fulvestrant component, based on a course duration of 13.3 months (14.46 cycles, per the financial estimates) and the same weighted DPMQ/DPMA for ribociclib and fulvestrant as above.

Estimated PBS usage & financial implications

- 4.26 The minor resubmission presented revised uptake rates as show in Table 5. Justification for the amended uptake rates were as follows:
- Population 1 (first-line, patients substituting RIBO+FULV for CDKI+NSAI). The PBAC previously considered this population was overestimated, as it was unlikely that patients would prefer a parenteral treatment (fulvestrant) over an oral NSAI. The resubmission argued that patients who failed an AI in the adjuvant setting are likely to prefer RIBO+FULV in the first line metastatic setting, but lowered these uptake estimates slightly.
 - Population 2 (first-line, growth of CDKI market from patients substituting for chemotherapy). The PBAC previously 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 very small proportion of patients currently receiving AI monotherapy would be suitable for second-line treatment with a CDKI. DUSC previously considered that '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'. The resubmission argued that there would be a small population believed to be endocrine resistant who would be considered suitable for RIBO+FULV due to the different mode of action of fulvestrant and reduced the proportion of patients who switch from chemotherapy to 5% annually. Consistent with the previous submission, no substitution from AI monotherapy was assumed. The PBAC noted that the uptake from patients substituting from chemotherapy was reduced as requested and considered that 5% uptake appeared to be a reasonable estimate.
 - Population 3 (second-line, patients displacing EVE+EXE). The PBAC previously considered that this population appeared to be overestimated as the previous submission assumed that growth in everolimus would be stable over the forward estimates, whereas DUSC noted that its use is declining. The resubmission

decreased the flat growth forecast of 0% for EVE + EXE to negative growth (0% in Year 1 decreasing to -10% growth in Year 6). The PBAC noted more recent data for everolimus in breast cancer (provided by the DUSC secretariat) indicated that the number of incident patients commencing everolimus was declining at an average of 13% per year over the 5 year period between 2015-16 and 2019-20. These data indicated that growth in the number of incident patients commencing everolimus was -15% in 2017-18, -26% in 2018-19 and -12% in 2019-20 for August to September in each period. The PBAC considered that the negative growth rates should be revised as shown in Table 5 based on the DUSC data, and assuming a decline in the annual negative growth of everolimus use consistent with the last 3 years of data for everolimus. The resubmission continued to assume that RIBO+FULV would substitute 80% (Year 1) to 95% (Year 4 onwards) of the use of everolimus (assuming 73.6% of all use of everolimus is in breast cancer). The pre-PBAC response argued that these uptake rates reflect the superior effectiveness and safety, and the lower treatment burden, of RIBO+FULV compared with EVE+EXE.

- Population 4 (second-line, patients displacing EXE only). The PBAC previously 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. In the resubmission, the uptake rates for patients on EXE monotherapy were reduced and tapered down year on year based on the reducing utilisation of the therapy in clinical practice. The PBAC considered that these changes appeared reasonable.
- 4.27 Many of the assumptions in estimating usage remained unjustified and uncertain.
- 4.28 DUSC previously noted 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. This approach was unchanged in the resubmission.
- 4.29 For the July 2020 submission, DUSC considered that the estimated growth in the CDKI market was overestimated. DUSC noted that this drug class had been PBS subsidised in Australia since July 2018 and up to 19% annual growth of the market is unlikely to be observed as the market was expected to have stabilised. The resubmission's estimated growth rates of 19% in 2021, 12% in 2022, and 6% in year from 2023 to 2026 were unchanged from the previous submission. This only had a minor impact on the financial estimates.

Public Summary Document – November 2020 PBAC Meeting

Table 5: Changes to uptake rates in the financial estimates

			Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Population	Changes		2021	2022	2023	2024	2025	2026
Population 1	% Substitution of current CDKI PATIENTS	From	20%	25%	30%	30%	30%	30%
		To	15%	20%	25%	28%	30%	30%
Population 2	Chemo switch %	From	10%	12%	14%	16%	18%	20%
		To	5%	5%	5%	5%	5%	5%
Population 3	Growth % forecast	From	0%	0%	0%	0%	0%	0%
		To	0%	-1%	-2%	-3%	-5%	-10%
	PBAC revised forecast		-14%	-13%	-11%	-9%	-7%	-6%
Population 4	Uptake - pts on EXE through PBS	From	50%	50%	50%	50%	50%	50%
		To	40%	40%	35%	20%	20%	10%

Source: Table 4, p 9 of the resubmission

4.30 The minor resubmission presented an analysis of uptake data from patients on a part-paid access program for access to RIBO+FULV. Patients in this program receive ribociclib free of charge but are required to self-fund fulvestrant for the duration of treatment. The resubmission stated that 90% of patients in the program are initiating treatment in the second-line treatment setting, and stated that this patient population is indicative of the eligible PBS second-line patient population. To estimate the patient numbers for the second line listing, the minor resubmission assumed a 50% increase in year 1 to account for additional patients for whom the financial burden of self-funding fulvestrant is prohibitive. The minor resubmission considered that this increase in patients is likely to be conservative as patient numbers are based on [REDACTED] oncologists registered with the program, of a total 622 Medical Oncologists in the Australian breast cancer setting. The number of second line patients in year 1 was estimated to be < 500. This was consistent with the number of second line patients calculated in the combined market share approach for this population (< 500). The pre-PBAC response provided updated data from the access program, which it stated further supported the uptake rates that were estimated for populations 3 and 4.

4.31 Using the proportions of prescriptions in first- and later-lines from the financial estimates (based on the relative proportions of prescriptions over the first 6 years of listing), the weighted price would be:

- 76% of total use of ribociclib (when used in combination with fulvestrant) would be in the first-line setting with an AEMP of \$ [REDACTED];
- 24% of total use of ribociclib (when used in combination with fulvestrant) would be in the second-line setting with an AEMP of \$ [REDACTED].

This would result in a weighted AEMP of \$ [REDACTED]. However, the resubmission offered a weighted AEMP of \$ [REDACTED], consistent with the current price for the existing listing.

Public Summary Document – November 2020 PBAC Meeting

This would equate to a relative weighting of 80%:20% in the first- and later-line settings, respectively. This lower AEMP was used in the financial estimates.

- 4.32 In the second-line setting, the PBAC previously considered that the key use of ribociclib would be prevalent patients who began treatment with AI monotherapy prior to listing of RIBO+NSAI, and that this would be a relatively small population. The PBAC considered that the relative weighting of 80%:20% applied in calculation of the proposed AEMP of \$ [REDACTED] was reasonable.
- 4.33 The minor resubmission estimated a net cost to the PBS/RPBS of \$10 million to < \$20 million in Year 6 of listing, with a total net cost to the PBS/RPBS of \$80 million to < \$90 million over the first 6 years of listing. This is summarised in the table below as well as the estimated patient and prescription numbers. The financial estimates have been revised to show the estimated extent of use and financial impact including the PBAC's revised estimates for population 3 as outlined in Table 5.
- 4.34 The resubmission used previous mark-ups when calculating the DPMQ (i.e. the financial estimates were based on a DPMQ of \$ [REDACTED] for ribociclib (600 mg), rather than \$ [REDACTED] using the July 2020 mark-ups). Using the current DPMQ results in a small increase to the overall financial estimates.

Public Summary Document – November 2020 PBAC Meeting

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
First line treatment						
Number of patients treated	■ ¹	■ ²	■ ²	■ ²	■ ²	■ ²
Number of ribociclib scripts dispensed	■ ³	■ ⁴	■ ⁴	■ ⁴	■ ⁵	■ ⁵
Second (and subsequent) line treatment						
Number of patients treated	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
PBAC revised patients	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Number of ribociclib scripts dispensed	■ ³	■ ³	■ ³	■ ²	■ ²	■ ²
PBAC revised ribociclib scripts	■ ³	■ ³	■ ³	■ ²	■ ²	■ ²
Annual proportion weighting (based on script numbers)						
First line	49%	65%	72%	79%	82%	87%
Second line	51%	35%	28%	21%	18%	13%
PBAC revised second line	50%	34%	27%	18%	16%	11%
Estimated financial implications of RIBO+FULV						
Total cost to PBS/RPBS for ribociclib	■ ⁶	■ ⁷	■ ⁸	■ ⁸	■ ⁸	■ ⁸
Total cost to PBS/RPBS for fulvestrant	■ ⁹	■ ⁹	■ ⁹	■ ⁹	■ ⁹	■ ⁹
Overall cost offsets	■ ⁹	■ ⁶	■ ⁷	■ ⁷	■ ⁸	■ ⁸
Total net cost to PBS/RPBS	■ ⁶	■ ⁶	■ ⁶	■ ⁶	■ ⁶	■ ⁶
PBAC revised total net cost to PBS/RPBS	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶	\$■ ⁶
Cost to MBS	-\$■ ⁹	-\$■ ⁹	-\$■ ⁹	-\$■ ⁹	-\$■ ⁹	-\$■ ⁹
Total net cost to PBS/RPBS/MB S	■ ⁶	■ ⁶	■ ⁶	■ ⁶	■ ⁶	■ ⁶
PBAC revised total cost to PBS/RPBS/MB S	■ ⁶	■ ⁶	■ ⁶	■ ⁶	■ ⁶	■ ⁶

Source: Table 6 of the resubmission, Section 4 financial estimates “Cost Summary” and “Offset Summary” worksheets

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ 10,000 to < 20,000

⁵ 20,000 to < 30,000

⁶ \$10 million to < \$20 million

Public Summary Document – November 2020 PBAC Meeting

⁷ \$20 million to < \$30 million

⁸ \$30 million to < \$40 million

⁹ \$0 to < \$10 million

4.35 The resubmission estimated that the total net cost to the PBS/RPBS over 6 years would be \$30 million to < \$40 million in the first-line setting and \$40 million to < \$50 million in the second-line setting (noting that offsets were higher in the first-line setting, with population 1 assumed to substitute for CDKIs in combination with NSAI). Applying the revised estimates for population 3, as considered appropriate by the PBAC, reduced the total net cost to the PBS/RPBS over 6 years in the second line setting to \$40 million to < \$50 million.

Financial Management – Risk Sharing Arrangements

4.36 The increases to the financial caps proposed in the July 2020 submission pre-PBAC response estimated a net cost to PBS/RPBS of \$100 million to < \$200 million over the first 6 years of listing.

4.37 The PBAC previously 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. To address this, population 1 was not included in the resubmission’s revised caps. The resubmission stated that populations 2, 3 and 4 are distinct from the existing patient population and should be added to the caps.

4.38 The proposed increase in the RSA caps for CDKIs is shown in Table 7. The proposed increases to the caps result in an increase of \$40 million to < \$50 million over 5 years, with the majority being from the cost for additional second line patients. Revised rates of everolimus growth as proposed by the PBAC reduced the increase in caps to \$40 million to < \$50 million over 5 years. For context, the existing first-line cap was set at \$200 million to < \$300 million over 5 years.

Table 7: Proposed increase in the RSA caps for the CDKIs

	Year 1	Year 2	Year 3	Year 4	Year 5
Population	2021	2022	2023	2024	2025
Ribociclib net impact – Population 1	■	■	■	■	■
Ribociclib cost to govt.- Population 2	■	■	■	■	■
Ribociclib cost to govt. - Population 3	■	■	■	■	■
Revised ribociclib cost to govt – Population 3	■	■	■	■	■
Ribociclib cost to govt. - Population 4	■	■	■	■	■
Total	■	■	■	■	■
PBAC revised total	■	■	■	■	■

Source: Table 7 of the resubmission. Shaded cells are values revised by PBAC

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the listing of ribociclib in combination with fulvestrant, for the treatment of patients with HR+, HER2- unresectable advanced or metastatic breast cancer. The PBAC previously recognised the clinical need for ribociclib in combination with fulvestrant but deferred making a recommendation in order to resolve the appropriate weighted price, financial impact and changes to risk sharing arrangements for ribociclib. The PBAC considered that these issues were appropriately addressed in the minor resubmission.
- 5.2 The PBAC noted it had previously indicated it was satisfied that RIBO+FULV is non-inferior to RIBO+NSAI in terms of PFS and that RIBO+FULV provides, for some patients, a significant improvement in PFS and a reduction in toxicity over EVE+EXE.
- 5.3 The PBAC recalled that, along with BCNA and MOGA, it had requested the sponsor submit an application for ribociclib in combination with fulvestrant in this indication. The PBAC previously recognised the high clinical need in the subsequent line listing, though use in this population is likely to be declining, and noted that there is also a need in the first line setting for patients who relapse on or within 12 months of prior (neo)adjuvant treatment with AI for early breast cancer and in the small group of patients in whom single-agent NSAIs may be used first line, but who are considered suitable for CDKI combination therapy in second line.
- 5.4 The PBAC recalled its July 2020 consideration of fulvestrant monotherapy and noted that fulvestrant would be acceptably cost-effective for use as monotherapy at the price proposed in this submission.
- 5.5 The PBAC considered there should be a single initial listing for ribociclib, combining first and subsequent line treatment, given ambiguity as to what constitutes the various 'lines' of therapy. The PBAC noted that this would result in ribociclib having a substantially different restriction to the other CDKIs, but considered this approach remained preferable. The PBAC considered grandfather and continuing restrictions combining first and subsequent line treatment would also be appropriate. The PBAC considered that the listing for fulvestrant should be a line-agnostic listing combining initial and continuing treatment, as recommended in its July 2020 consideration of fulvestrant.
- 5.6 The PBAC noted that the approach to the cost minimisation analysis and the price derived for RIBO+FULV compared with RIBO+NSAI as first line treatment was unchanged from the July 2020 submission. The PBAC previously considered that the proposed equi-effective doses were reasonable. The PBAC noted that the comparator price applied in the cost-minimisation analysis did not take into account the cost-effective net cost of RIBO+NSAI as it did not include the rebates that were intended to be achieved through the financial caps, noting the existing CDKI caps were intended to be exceeded by 22% in order to achieve a cost-effective net cost for RIBO+NSAI.

However, the PBAC noted that the requested price of ribociclib (for use in combination with fulvestrant) is 22% lower than in the existing listing. Thus, based on the ribociclib component alone the proposed AEMP in the first-line setting was consistent with the intended cost-effective price for the existing listing of ribociclib, though not when the cost of concomitant therapies are taken into account. The PBAC considered that the proposed price for ribociclib in the first line setting was acceptable in the context of a range of factors including the overall weighted price proposed, the proposed price in this submission for fulvestrant, and given that the current CDKI caps are expected to be exceeded in years 3-5.

- 5.7 The July 2020 submission also presented a cost-effectiveness analysis for RIBO+FULV versus EVE+EXE in second/subsequent line treatment. The PBAC requested two changes to this model: a 7-year time horizon; and use of observed K-M data up to the time point at which the observed data becomes unreliable and adjusting the extrapolation of survival data. The PBAC also advised that the price should be reduced in order to achieve an ICER of <\$55,000 to < \$75,000 per QALY in this setting. The PBAC recalled it considered this ICER would be acceptable in the context of a small and decreasing second line population (paragraph 7.18, ribociclib PSD, July 2020 PBAC meeting). The PBAC also recalled 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 (paragraph 7.15, ribociclib PSD, July 2020 PBAC meeting).
- 5.8 The PBAC noted that the resubmission accepted the 7-year time horizon in the context of the uncertain comparative data. However, the resubmission proposed an alternative method of extrapolating the K-M data. The July 2020 evaluator's methodology used K-M data up to the point of median PFS/OS, while the resubmission argued that it would be more appropriate to use K-M data up to the point at which 20% of patients are at risk of an event. Overall, the PBAC considered that the resubmission's approach resulted in survival curves that had good visual fit to the observed data and appeared reasonable.
- 5.9 Overall, the PBAC considered the prices proposed in each of the settings were reasonable, and the resubmission's overall proposal of a price that is the same as the current price for use in combination with NSAI was appropriate.
- 5.10 The PBAC recalled that it previously considered that many of the assumptions used in the financial estimates were uncertain and likely to have substantially overestimated the number of treated patients (paragraph 7.19 ribociclib PSD, July 2020 PBAC meeting). The PBAC noted that the resubmission presented revised uptake rates and considered that the changes in utilisation appeared reasonable, with the exception of the rates of EVE+EXE growth as applied to estimate population 3. The PBAC considered that DUSC data for everolimus use in breast cancer indicated that use was continuing to decline more rapidly than assumed in the resubmission. The PBAC considered that the negative growth rates should be revised based on these DUSC data, and assuming a decline in the annual negative growth of everolimus use consistent with the last 3

years of data for everolimus.

- 5.11 The resubmission estimated that the total net cost to the PBS/RPBS over 6 years would be \$30 million to < \$40 million in the first-line setting and \$40 million to < \$50 million in the second-line setting (noting that offsets were higher in the first-line setting, with population 1 assumed to substitute for CDKIs in combination with NSAIs). Applying the revised estimates for population 3, as considered appropriate by the PBAC, reduced the total net cost to the PBS/RPBS over 6 years in the second line setting to \$40 million to < \$50 million. With these revised estimates the total net cost to PBS/RPBS was reduced from \$80 million to < \$90 million to \$80 million to < \$90 million over the first 6 years of listing.
- 5.12 In the second-line setting, the PBAC previously considered that the key use of ribociclib would be in prevalent patients who began treatment with AI monotherapy prior to listing of RIBO+NSAI, and that this would be a relatively small population. The PBAC noted that the weighting of first and second line use was revised as requested. The PBAC considered that the overall relative weighting of 80% first line scripts to 20% second line scripts, applied in calculating the proposed weighted AEMP for ribociclib of \$ [REDACTED], was reasonable.
- 5.13 The PBAC recalled that it previously considered that the total increase in the CDKI market as a result of listing RIBO+FULV would be very small and overall only a small increase in financial caps would be justifiable (paragraph 7.23, ribociclib PSD, July 2020 Meeting). The PBAC noted that the July 2020 submission requested a \$90 million to < \$100 million increase to the current CDKI caps over the first 5 years (table 23, ribociclib PSD, July 2020 PBAC Meeting). The resubmission estimated a net increase to the existing caps of \$40 million to < \$50 million which was reduced to \$40 million to < \$50 million when the PBAC's revised population 3 estimates were applied. The PBAC noted that the majority of this increase was due to additional costs for patients receiving second line treatment, which is likely to decline as a proportion of overall use.
- 5.14 The PBAC considered that no changes to the listings for other CDKIs were required and changes to allow combination use with fulvestrant as a combined first and subsequent line listing should only apply to ribociclib.
- 5.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for fulvestrant:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over combination use with NSAIs or current subsequent line treatments. The PBAC considered this criteria was not met as the available data did not allow a reliable assessment of the magnitude of the incremental benefit;

Public Summary Document – November 2020 PBAC Meeting

- b) The treatment is not expected to address a high and urgent unmet clinical need; and
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

5.16 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Amend existing listing as follows (changes to existing first-line listing are shown in strike-through and italics):

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RIBOCICLIB					
ribociclib 200 mg tablet, 21	11385F	1	21	5	Kisqali
ribociclib 200 mg tablet, 63	11386G	1	63	5	Kisqali
ribociclib 200 mg tablet, 42	11397W	1	42	5	Kisqali
<i>Unshaded rows indicate common concepts across all 3 pack sizes</i>					
Restriction Summary 10055 / ToC: 10037: Authority Required – 21 tablet pack					
Restriction Summary 10060 / ToC: 10018: Authority Required – 63 tablet pack					
Restriction Summary 10056 / ToC: 10044: Authority Required – 42 tablet pack					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)				
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Indication: Locally advanced or metastatic breast cancer				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	Patient must not have previously been treated with an aromatase inhibitor for advanced or metastatic breast cancer				
	AND				
	Clinical criteria:				
	Patient must not have previously been treated with abemaciclib or palbociclib; or				
	Patient must be untreated with each of: (i) abemaciclib, (ii) palbociclib, (iii) ribociclib; or				
	Patient must have developed an intolerance to abemaciclib or palbociclib of a severity necessitating permanent treatment withdrawal				
	AND				

Public Summary Document – November 2020 PBAC Meeting

Clinical criteria:
The condition must be hormone receptor positive
AND
Clinical criteria:
The condition must be human epidermal growth factor receptor 2 (HER2) negative
AND
Clinical criteria:
The condition must be inoperable
AND
Clinical criteria:
Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less
AND
Clinical criteria:
The treatment must be in combination with anastrozole or letrozole
<i>Where the patient has never been treated with endocrine therapy for advanced/metastatic disease, the treatment must be in combination with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant; or</i>
<i>Where the patient has recurrence/progressive disease despite being treated with endocrine therapy for advanced/metastatic disease, the treatment must be in combination with fulvestrant only</i>
AND
Clinical criteria:
The treatment must not be in combination with abemaciclib or palbociclib
AND
Clinical criteria:
Patient must require dosage reduction requiring a pack of 21 tablets
Clinical criteria:
Patient must require dosage reduction requiring a pack of 42 tablets
AND
Population criteria:
Patient must not be premenopausal
Caution: QT interval monitoring is required for patients treated with this drug.
Restriction Summary 10016 / ToC: 10038: Authority Required – 21 tablet pack
Restriction Summary 10017 / ToC: 10057: Authority Required – 63 tablet pack
Restriction Summary 10031 / ToC: 10054: Authority Required – 42 tablet pack
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Indication: Locally advanced or metastatic breast cancer
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not develop disease progression while receiving treatment with this drug for this condition
Patient must not have developed disease progression while being treated with this drug for this condition
AND
Clinical criteria:
Patient must have stable or responding disease

Public Summary Document – November 2020 PBAC Meeting

	AND
	Clinical criteria:
	The treatment must be in combination with anastrozole or letrozole
	The treatment must be in combination with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant
	AND
	Clinical criteria:
	The treatment must not be in combination with abemaciclib or palbociclib
	AND
	Clinical criteria:
	Patient must require dosage reduction requiring a pack of 21 tablets
	Clinical criteria:
	Patient must require dosage reduction requiring a pack of 42 tablets
	AND
	Population criteria:
	Patient must not be premenopausal
	Caution: QT interval monitoring is required for patients treated with this drug.
	Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS subsidised treatment with this drug.
Add new Restriction Summary / ToC: Authority Required – 21 tablet pack	
Add new Restriction Summary / ToC: Authority Required – 63 tablet pack	
Add new Restriction Summary / ToC: Authority Required – 42 tablet pack	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Indication: Locally advanced or metastatic breast cancer
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - 'Grandfather' treatment
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this PBS-indication prior to [insert date of PBS listing]
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition
	AND
	Clinical criteria:
	Patient must have been untreated with each of: (i) abemaciclib, (ii) palbociclib, (iii) ribociclib, at the time non-PBS supply was initiated; or
	Patient must have developed an intolerance to abemaciclib or palbociclib of a severity necessitating permanent treatment withdrawal
	AND
	Clinical criteria:
	The condition must be hormone receptor positive
	AND

Public Summary Document – November 2020 PBAC Meeting

	Clinical criteria:
	The condition must be human epidermal growth factor receptor 2 (HER2) negative
	AND
	Clinical criteria:
	The condition must be inoperable
	AND
	Clinical criteria:
	Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 2 at the time of non-PBS supply was initiated
	AND
	Clinical criteria:
	The treatment must be in combination with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant, where the patient had never been treated with endocrine therapy for advanced/metastatic disease at the time non-PBS supply was initiated; or
	The treatment must be in combination with fulvestrant only, where at the time non-PBS supply was initiated, the patient had recurrent/progressive disease despite being treated with endocrine therapy for advanced/metastatic disease
	AND
	Clinical criteria:
	The treatment must not be in combination with abemaciclib or palbociclib
	AND
	Clinical criteria:
	Patient must require dosage reduction requiring a pack of 21 tablets
	Clinical criteria:
	Patient must require dosage reduction requiring a pack of 42 tablets
	AND
	Population criteria:
	Patient must not be premenopausal
	Caution: QT interval monitoring is required for patients treated with this drug.

6.2 Extend the July 2020 PBAC recommendation to list AstraZeneca Pty Ltd's 'Faslodex' branded product of fulvestrant to also include Sandoz Pty Ltd's 'Fulvestrant Sandoz' branded product of fulvestrant, with the same PBS listing as outlined in the July 2020 PSD as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
FULVESTRANT fulvestrant 250 mg/5 mL pre-filled syringe, 2	NEW	1	1	5	Faslodex [recommended in July 2020, but not available on the PBS as of 1 November 2020] Fulvestrant Sandoz
Restriction Summary NEW / ToC: NEW					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Type: <input type="checkbox"/> Authority Required – Streamlined [new code]				
	Administrative Advice: Special pricing arrangements apply				
	Indication: Locally advanced or metastatic breast cancer				

	Clinical criteria:
	The condition must be hormone receptor positive
	AND
	Clinical criteria:
	The condition must be human epidermal growth factor receptor 2 (HER2) negative
	AND
	Clinical criteria:
	The condition must be inoperable
	AND
	Population criteria:
	Patient must not be premenopausal
	Prescriber Instructions:
	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.

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

7 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.

8 Sponsor's Comment

Novartis welcomes the PBAC's decision to recommend ribociclib in combination with fulvestrant for the treatment of patients with HR+ and HER2-, advanced/metastatic breast cancer.