

## 7.08 RIBOCICLIB, Tablet 200mg, Kisqali<sup>®</sup>, Novartis Pharmaceuticals Australia Pty Ltd

### 1 Purpose of application

- 1.1 Section 85, Authority Required listing for ribociclib in combination with a non-steroidal aromatase inhibitor (NSAI) for first-line endocrine based treatment of patients with non-premenopausal, hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC). The PBAC previously considered an application for ribociclib for this indication at the July 2017 meeting.
- 1.2 The requested basis for listing was a cost-utility analysis for ribociclib + letrozole compared with letrozole alone. The re-submission also presented a cost-minimisation analysis compared with a near market comparator, palbociclib plus letrozole, which was on the agenda for a similar indication at the November 2017 meeting.

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

Component	Description
Population	Postmenopausal patients with hormone receptor positive (HR+)/ human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer
Intervention	Ribociclib (600 mg on days 1-21 of a 28-day cycle) + letrozole (2.5 mg on days 1-28 of a 28-day cycle)
Comparator	1 Placebo + letrozole (2.5 mg on days 1-28 of a 28-day cycle); OR 2 Palbociclib (125 mg on days 1-21 of a 28-day cycle) + letrozole (2.5 mg on days 1-28 of a 28-day cycle)
Outcomes	Change in progression free survival (PFS) Overall survival (OS) Overall Response Rate (ORR) Health related quality of life (HRQoL) Serious adverse events (SAE)
Clinical claim	In postmenopausal women with hormone receptor positive (HR+)/ human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer: 1 Ribociclib + letrozole provides superior effectiveness and inferior safety to letrozole alone; AND 2 Ribociclib + letrozole provides non-inferior effectiveness and safety to palbociclib + letrozole

Source: Table 1.1, p32 of the re-submission

## 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RIBOCICLIB Tablet, 200mg	63		Published price: \$ [REDACTED] Effective price: \$ [REDACTED]	Kisqali Novartis Pharmaceuticals Australia Pty Ltd
	42	5	Published price: \$ [REDACTED] Effective price: \$ [REDACTED]	
	21		Published price: \$ [REDACTED] Effective price: \$ [REDACTED]	

Category / Program:	Section 85
PBS Indication:	Locally advanced inoperable and metastatic breast cancer
Treatment phase:	Initial
Restriction:	Authority required – In Writing (Initial) Authority required – Telephone (Continuing)
Treatment criteria:	The treatment must be an initial endocrine-based therapy for this indication. AND The treatment must be in combination with a non-steroidal aromatase inhibitor (NSAI).
Clinical criteria:	The condition must be hormone receptor positive. AND The condition must be human epidermal growth factor receptor 2 (HER2) negative. AND Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or less. AND Patient must not have inflammatory breast cancer or uncontrolled brain metastases.
Population criteria:	Patient must not be premenopausal. Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LHRHa) (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression for patients receiving PBS ribociclib. <del>Patients who progress during first five years of adjuvant endocrine therapy are not eligible for reimbursed ribociclib.</del> [Proposed in the Pre-Sub-Committee Response (PSCR) (p1)]
Prescriber Instructions	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. Authority applications for treatment must be made in writing.

- 2.1 The re-submission changed the 'PBS Indication' from 'advanced or metastatic' to 'locally advanced inoperable and metastatic breast cancer'. This is in line with the PBAC's previous consideration (PSD, July 2017, item 2.1 and 7.3).
- 2.2 The re-submission changed the restriction to allow ribociclib to be used in combination with all NSAIs and not just letrozole as previously proposed. This is in line with the PBAC's previous consideration (PSD, July 2017, item 2.1 and 7.4).
- 2.3 The re-submission added that patients must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or less. This is in line with the PBAC's previous consideration (PSD, July 2017, item 2.1 and item 7.5). The Pre-Sub-Committee Response (PSCR) (p1) noted that the PBAC's suggested listing for palbociclib allows inclusion of patients with ECOG performance

status of 2 (paragraph 7.4 of Public Summary Document (PSD) from March 2017). The PSCR acknowledged that MONALEESA-2 did not include patients with ECOG status of 2 or more, however, it is also noted that PALOMA-2 only included <2% of patients with ECOG status of 2. The sponsor requested the PBAC acknowledge the equivalent efficacy of these agents and apply restrictions based on ECOG consistently across the class.

- 2.4 The re-submission added that patients must not have undergone ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LHRHa) (goserelin acetate or leuprolide acetate) for induction of ovarian suppression. This is in line with the PBAC's previous consideration (PSD, July 2017, item 7.5).
- 2.5 The re-submission added that patients must not have inflammatory breast cancer or uncontrolled brain metastases. This is in line with the PBAC's previous consideration (PSD, July 2017, item 7.5).
- 2.6 The re-submission added that patients who progress during the first five years of adjuvant endocrine therapy are not eligible for reimbursed ribociclib. In MONALEESA-2, patients were included if they had received prior (neo) adjuvant therapy which included letrozole or anastrozole, although the disease-free interval had to be greater than 12 months. The re-submission explained that this was due to ethical reasons (it would have been unethical to treat these patients with letrozole alone). The proposed PBS restriction aims to exclude patients who are truly 'endocrine resistant'. The PSCR (p1) proposed in the event that the PBAC determines it is important to clarify eligibility regarding response to adjuvant endocrine therapy, the sponsor recommends the following text (for both ribociclib and palbociclib) based on discussion with clinicians and the eligibility criteria of the respective, pivotal RCTs.
  - Removal of the text: "Patient must not progress during the first 5 years of adjuvant endocrine therapy".
  - Addition of text: Patients with 'primary resistance' to adjuvant non-steroidal aromatase inhibitors (NSAIs) are not eligible for reimbursed ribociclib.
  - Addition of text: Primary resistance is defined as: patients not responding to initial (2 years) NSAI therapy, patients who relapse during the first 2 years of adjuvant NSAI therapy or patients who have a progression of disease within 6 months of the beginning of first-line therapy with an NSAI. (The definition was derived from Pronzato, 'Role of everolimus in the treatment of metastatic HER2-negative/HR-positive breast cancer, Future Oncol. (2017) 13:1371–1384, provided with the PSCR).

The PSCR argued that it is important to change the proposed criteria from adjuvant endocrine therapy to adjuvant NSAI's because patients relapsing after adjuvant tamoxifen or exemestane were not excluded from MONALEESA-2 (or PALOMA-2). Clinicians believe the above criteria for "primary resistance" better defines patients who are 'truly' NSAI resistant than the MONALEESA-2 disease-free interval criteria. Clinicians want to avoid exclusion of patients with only 'acquired' NSAI resistance after receiving a good response to adjuvant NSAI therapy and who may receive benefit from the combination of ribociclib and NSAI. It is not expected that they

would treat patients with “primary resistance to adjuvant NSAIs”. In making these suggestions to the PBAC, the sponsor assumed that based on palbociclib having the same eligibility criteria with regards to treatment free interval after adjuvant AI, that decision making will be made on behalf of the class and the same listing criteria will be applied for both agents.

2.7 The re-submission also requested an initial grandfather restriction to cover those patients who are currently receiving ribociclib + letrozole [REDACTED] and patients who have received  $\leq 28$  days of treatment with a NSAID via the PBS. The proposed grandfather restriction differs from the previous submission in that it:

- Added “Authority Required – In Writing”, which is in addition to “Authority Required – Telephone” and “Authority Required – Electronic”. The evaluation noted that this is not appropriate.
- Changed the restriction to allow ribociclib to be used in combination with all NSAIDs and not just letrozole as initially proposed. This is appropriate.
- Added “Patients who have received  $\leq 28$  days of treatment with a NSAID for their locally advanced inoperable or metastatic breast cancer are not excluded from PBS ribociclib”. The evaluation noted that this is reasonable.
- Removed “Patients with progressive disease with ribociclib are no longer eligible for PBS-subsidised ribociclib”. The evaluation noted that this is not appropriate.

2.8 The grandfather restriction is broader than the initial restriction. There is no restriction regarding ECOG status, inflammatory breast cancer, ovarian suppression, and progression during first 5 years of adjuvant endocrine therapy.

2.9 The re-submission proposed continuation criteria for ribociclib. The criteria are consistent with the RECIST 1.1 criteria that are used in MONALEESA-2. This definition of RECIST1.1 in the proposed restriction is different to text currently used for listing on the PBS.

2.10 The re-submission proposed an effective price for ribociclib which is [REDACTED]% - [REDACTED]% lower than the previous submission, depending on the pack size.

2.11 The re-submission again included a request for a special pricing arrangement, where the proposed effective prices are [REDACTED]% - [REDACTED]% lower than the published prices, depending on the pack size.

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

### **3 Background**

#### **Registration status**

3.1 Ribociclib was TGA registered on 23 October 2017 for the following indication:

*KISQALI [ribociclib] in combination with an aromatase inhibitor is indicated for the treatment of men and postmenopausal women with hormone receptor positive*

*(HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer, as an initial endocrine-based therapy.*

## Previous PBAC consideration

3.2 In July 2017 the PBAC did not recommend the listing of ribociclib on the PBS as initial endocrine-based therapy for patients with non premenopausal, HR+, HER2- advanced breast cancer on the basis of unfavourable and uncertain cost-effectiveness, and uncertainties regarding the magnitude of incremental benefit of ribociclib (PSD, July 2017, item 7.1).

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

**Table 2: Summary of outstanding matters of concern**

Matter of concern	How the resubmission addresses it
<p><b>Comparator</b></p> <p>The submission proposed letrozole alone as the main comparator on the basis that letrozole is the most commonly prescribed first line therapy for HR+, HER2- ABC. The PBAC considered that an NSAI (i.e. letrozole or anastrozole) alone was the appropriate comparator for ribociclib + NSAI. The PBAC considered that on balance in clinical practice, it would be reasonable to expect that letrozole or anastrozole would provide a similar benefit in combination with ribociclib. The PBAC also considered that palbociclib was an appropriate near market comparator, as it is of the same therapeutic class with similar indication. (PSD, July 2017, item 7.8).</p>	<p>The comparators remained unchanged (main: letrozole alone and near market: palbociclib).</p>
<p><b>Clinical claim versus letrozole alone</b></p> <p>The PBAC considered that the chief limitations of the MONALEESA-2 trial were that it was not adequately powered for OS, and initial results were based on an interim analysis of the trial. The PBAC noted that the final OS analysis is unlikely to be available until 2020. Notwithstanding these limitations, the PBAC noted that the MONALEESA-2 trial demonstrated improvement in median PFS by 9 months (based on median follow-up of around 20 months). However, the PBAC noted that there was no significant difference in OS, and that the survival data were immature, given that the survival curves diverged at a point where the number of patients at risk was too small to draw any meaningful conclusions. As such, the PBAC advised that while the submission's claim of superior efficacy against letrozole alone was likely to be reasonable for PFS, the immaturity of the OS data resulted in a high degree of uncertainty in the assessment of its magnitude of long-term benefit. The PBAC also noted that ribociclib was not associated with improvement in quality of life. (PSD, July 2017, item 7.9).</p>	<p>The re-submission provided the following additional post-hoc analyses based on the January 2017 data cut-off of the MONALEESA-2 trial:</p> <ul style="list-style-type: none"> <li>• Best overall response,</li> <li>• Incidence of AEs, and</li> <li>• Dose reductions.</li> </ul> <p>Clinical claim versus letrozole alone unchanged.</p>
<p><b>Clinical claim versus palbociclib</b></p> <p>The PBAC noted that the indirect comparison against palbociclib presented in the submission did not demonstrate a significant difference in PFS. However, the PBAC considered that lack of evidence of a significant difference is not equivalent to evidence of no difference (non-inferiority). Furthermore, there was limited exchangeability across MONALEESA-1 (ribociclib) and PALOMA-1 and PALOMA-2 (palbociclib) trials. The PBAC also noted that there were significantly more treatment discontinuations resulting from AEs for ribociclib plus letrozole compared with palbociclib plus letrozole. Overall, the PBAC advised that there was limited data to support the submission's claim of non-inferiority in effectiveness and safety</p>	<p>The re-submission revised the indirect comparison and compared the MONALEESA-2 trial to the PALOMA-2 trial only, using placebo + letrozole as the common comparator.</p> <p>The clinical claim was changed from "Ribociclib + letrozole provides non-inferior effectiveness and safety to palbociclib + letrozole" to "Ribociclib + letrozole provides similar effectiveness and safety to palbociclib + letrozole".</p>

Matter of concern	How the resubmission addresses it
compared with palbociclib. (PSD, July 2017, item 7.12).	
<p><b>Economic evidence – cost-effectiveness</b></p> <p>The PBAC noted that the PSCR provided an updated economic model based on the January 2017 interim data analysis, which reported an ICER of \$75,000/QALY - \$105,000/QALY gained. The PBAC considered that although the use of the updated data addressed some of the issues raised in the evaluation, the ICER from the PSCR could not be directly compared with the ICER from the submission (of \$105,000/QALY - \$200,000/QALY gained) as the extrapolation approach differed between the two economic models. Additionally, the PBAC noted that the ICER provided in the PSCR was sensitive to the choice of functional form for the extrapolation. The PBAC therefore advised that the updated model required evaluation via a subsequent major submission. (PSD, July 2017, item 7.13).</p>	The re-submission provided an updated economic model.
<p><b>Economic evidence – time horizon in cost-effectiveness model</b></p> <p>In addition, the PBAC considered that a time horizon no more than 5 years would be appropriate, given the immaturity of the existing survival data and resulting uncertainties surrounding a potential OS benefit. The PBAC noted that the results of the economic model presented in the submission were highly sensitive to the time horizon. (PSD, July 2017, item 7.14).</p>	The time horizon was unchanged from 10 years.
<p><b>Economic evidence – cost-minimisation</b></p> <p>The relative dose intensity (RDI) applied in the cost-minimisation analysis was lower for ribociclib than for palbociclib due to patients experiencing more AEs requiring a dose reduction with ribociclib. The lower RDI is inconsistent with the claim of non-inferior safety between ribociclib + letrozole and palbociclib plus letrozole. It also results in the price for ribociclib being higher than if the same RDI was applied to ribociclib and palbociclib. (PSD, July 2017, item 6.43).</p>	The re-submission reduced the RDI applied from █% (based on the mean RDI in MONALEESA-2 in the January 2016 interim analysis) to █% (based on the median RDI in MONALEESA-2 in the January 2017 interim analysis). The lower RDI is inconsistent with the claim of non-inferior safety between ribociclib + letrozole and palbociclib plus letrozole.
<p><b>Financial estimates</b></p> <p>The uptake rate of █% was considered to be high and uncertain as there was a lack of detail on the clinical expert opinion that was sought by the submission to inform this assumption. (PSD, July 2017, item 6.48).</p>	Reduced uptake to █% in Year 1, █% in Year 2, █% in Year 3 and █% from Years 4-6 (vs. █% in every year in the July 2017 submission). The estimate remains uncertain.
<p>The estimate of the number of prescriptions per patient per year (10.5) was uncertain as it was based on interim results for the mean relative dose intensity from the MONALEESA-2 trial. The dose intensity in practice may differ to that observed in the clinical trial. (PSD, July 2017, item 6.48).</p>	Reduced the average dose of █ mg (vs. █ mg in the July 2017 submission) based on the January 2017 interim analysis of MONALEESA-2, and took into account the dispensing of the three pack sizes (21, 42 and 63 tablet packs). The dose intensity in practice may differ to that observed in the clinical trial.
<p>The assumption for the annual growth in the eligible population (█%) was a likely overestimate. It was based on the uptake of letrozole that is used to treat a wider range of cancers than ribociclib. (PSD, July 2017, item 6.48).</p>	Reduced the growth rate of the eligible population of █%. Average growth in breast cancer incidence from 2009-13 was 3.3%pa <sup>1</sup> . The growth rate may be over-estimated.
<p>Under the proposed TGA indication, ribociclib plus letrozole is intended for use as an initial endocrine-based therapy. There is a risk of use in people who have previously been treated, or are currently being treated, with letrozole and anastrozole at the time of ribociclib's listing. This issue is likely to be most relevant for the first year of listing. (PSD, July 2017, item 6.48).</p>	Not addressed.
There is a risk of continued use of ribociclib following disease	The re-submission proposed continuation criteria for

<sup>1</sup> AIHW (2016) Australian Cancer Incidence and Mortality (ACIM) books. <http://www.aihw.gov.au/acim-books/>

Matter of concern	How the resubmission addresses it
progression as the continuation criteria is not based on an objective measure. (PSD, July 2017, item 6.48).	ribociclib. However, it is unclear how these continuation criteria will be incorporated into the restriction.
Additional medicine costs to treat adverse events associated with ribociclib were not included. (PSD, July 2017, item 6.48).	Not addressed.
<p><b>Future re-submissions</b></p> <p>The PBAC further advised that for ribociclib to be considered acceptably cost-effective, in the context of the risk of the gain in PFS not adequately translating to a subsequent incremental OS and the relatively insignificant quality of life gain associated with the PFS benefit, a substantial price reduction would likely be required. (PSD, July 2017, item 7.18).</p> <p>The PBAC indicated that it would be open to considering a recommendation for ribociclib for PBS listing under an appropriate arrangement pending further OS data, should evidence compelling it to do so be presented in a future major resubmission. (PSD, July 2017, item 7.19).</p>	Price reduction proposed. No risk-share arrangement proposed.

ABC: Advanced breast cancer; AE: Adverse event; HR+: Hormone receptor positive; HER2-: human epidermal growth factor receptor 2 negative; ICER: Incremental cost-effectiveness ratio; NSAI: non-steroidal aromatase inhibitor; OS: Overall survival; PFS: Progression-free survival; PSCR: Pre sub-committee response; QALY: Quality adjusted life year; RDI: Relative dose intensity; TGA: Therapeutic Goods Administration.

- 3.4 Palbociclib, a near market comparator, was not recommended by the PBAC at the March 2017 meeting for the initial endocrine treatment of hormone receptor HR+, HER2- ABC in combination with letrozole. A major re-submission of palbociclib was considered by the PBAC for a similar indication at the November 2017 meeting.

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

## 4 Population and disease

- 4.1 Breast cancer is among the most commonly diagnosed cancers in Australia. The most common form of breast cancer is the HR+/HER- molecular subtype, which is associated with favourable prognosis due to its responsiveness to hormonal/endocrine therapy. However, development of endocrine resistance is limiting the efficacy of current therapies, which eventually leads to disease progression.
- 4.2 The re-submission proposed the addition of ribociclib, in combination with an NSAI, for the treatment of non-premenopausal, HR+ and HER2-, ABC patients currently treated with NSAI as first-line endocrine-based therapy.

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

## 5 Comparator

- 5.1 The re-submission nominated letrozole alone as the main comparator. This is unchanged from the previous submission. The PBAC previously considered that the main comparator should be a NSAI (i.e. letrozole or anastrozole) (PSD, July 2017, item 7.8).

- 5.2 The re-submission nominated palbociclib as a secondary (near market) comparator. This is unchanged from the previous submission. The PBAC previously considered that this is an appropriate near market comparator (PSD, July 2017, item 7.8).

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (25) and organisations (1) via the Consumer Comments facility on the PBS website. The comments were similar to those received when the original ribociclib submission was considered, and noted that ribociclib could help improve breast cancer patients' quality of life but there is currently a high financial cost. The PBAC noted a difference in the number of inputs submitted for this medicine compared with palbociclib, but interpreted this as meaning general support for CDK4/6 inhibitors.
- 6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) supporting the listing of ribociclib. The PBAC specifically noted the claim that the use of ribociclib may improve quality of life and result in time and financial savings to both the health system and patients. The BCNA also noted evidence presented at the American Society of Clinical Oncology (ASCO) Annual Scientific Meeting from the MONALEESA-2 trial which showed progression-free survival for women treated with ribociclib continues to improve as the data matures.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the ribociclib submission, on the basis of improved progression free survival (PFS). The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for ribociclib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>[1]</sup>, based on a comparison with NSAI alone. When ribociclib was considered at the July 2017 meeting it received a score of 2, based on the previous version of the Scale. The MOGA noted that if future analysis demonstrates a survival benefit for ribociclib in combination with letrozole, the ESMO-MCBS score may increase to 4.

### ***Clinical trials***

- 6.5 The re-submission was based on direct evidence from one head-to-head phase III randomised, double-blind trial comparing ribociclib + letrozole to letrozole alone in postmenopausal women with HR+, HER2- ABC (MONALEESA-2). This is unchanged from the previous submission.

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

- 6.6 In addition two randomised trials were provided as part of an indirect secondary comparison between ribociclib and palbociclib.
- PALOMA-1: a phase II, randomised, open-label trial of palbociclib + letrozole for first line treatment of oestrogen receptor positive (ER+), HER2- ABC in postmenopausal women.
  - PALOMA-2: a phase III, randomised, double-blind trial of palbociclib + letrozole for first line treatment of ER+, HER2- ABC in postmenopausal women.
- 6.7 The re-submission presented an indirect comparison to palbociclib by comparing the MONALEESA-2 trial (January 2017 data cut-off) to the PALOMA-2 trial only, using placebo + letrozole as the common comparator. This is changed from the previous submission, which presented six different indirect comparisons based on use of PALOMA-1 alone, PALOMA-2 alone, meta-analysis of PALOMA-1 and 2 and use of MONALEESA-2 January and June 2016 interim results.
- 6.8 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial vs placebo</b>		
MONALEESA-2 NCT01958021 CLEE011A2301 2013-003084-61	Title: 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.	
	Interim Clinical Study Report (CSR): Data cut off 29 Jan 2016, report date 27 July 2016.	27 July 2016
	Executive Summary for interim 90 Day Update: Data cut off 18 Aug 2016, report date 13 Sep 2016.	13 Sept 2016
	Second Overall Survival Interim Analysis: Data cut off 2 Jan 2017, report date 11 Feb 2017.	11 Feb 2017
	Publication: Hortobagyi, Stemmer et al. 2016. Ribociclib as First line Therapy for HR-Positive, Advanced Breast Cancer.	NEJM 2016; 375 (17): 38-48
<b>Supplementary randomised trials for indirect comparison: palbociclib plus letrozole vs letrozole alone</b>		
PALOMA-1 A5481003 [NCT00721409]	Finn, RS Crown, JP Lang, I et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.	Lancet Oncol 2015; 16:25-35.
	Finn, RS Crown, JP, Ettl J et al. Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomised pivotal trial PALOMA-1/TRIO-18.	Breast Cancer Research (2016) 18:67.
	Bell, Crown et al. 2016. Impact of palbociclib plus letrozole on pain severity and pain interference with daily activities in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer as first line treatment	Current Medical Research and Opinion 2016; 32:5, 959-965.
PALOMA-2 NCT01740427 A5481008, 2012-004601-27	Finn, Martin et al. 2016. Palbociclib and Letrozole in Advanced Breast Cancer.	NEJM 2016; 375: 1925-1936.
	Finn, RS Martin, M Hope, S et al. PALOMA-2: Primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2– advanced breast cancer (ABC). Rugo 2016. Impact of palbociclib plus letrozole on health related quality of life (HRQOL) compared with letrozole alone in treatment naïve postmenopausal patients with ER+ HER2-metastatic breast cancer (MBC): Results from PALOMA-2. An Oncol 27 (suppl_6): 225PD	J Clin Oncol 34, 2016 (suppl; abstract 507). An Oncol 27 (suppl_6): 225PD

Source: Table 2.1, p50 of the re-submission

6.9 The key features of the direct and supplementary randomised trial are summarised in the table below.

**Table 4: Key features of the included evidence, ribociclib + letrozole vs letrozole alone**

Trial	N	Design/ duration of follow-up (median)	Risk of bias	Patient population	Outcomes presented in Section 2	Use in modelled evaluation in Section 3
<b>DIRECT EVIDENCE: Ribociclib + letrozole vs letrozole</b>						
<b>MONALEESA-2</b>	668	R, DB, MC	Low	Treatment naïve HR+/HER2- ABC		
-Jan 2016 interim analysis		15.3 months			Primary: investigator assessed PFS Secondary: BICR PFS, ORR, CBR, OS, AEs, PROs	Not used
-Jun 2016 interim analysis		20.1 months			Primary: investigator assessed PFS Secondary: ORR, CBR, AEs	ORR and AEs used in indirect comparison for cost-minimisation.
-Jan 2017 interim analysis		26.4 months			Primary: investigator assessed PFS Secondary: OS	PFS, ORR, OS, TTD and AEs used in economic model. PFS used in indirect comparison for cost- minimisation.
<b>INDIRECT EVIDENCE: Palbociclib + letrozole vs letrozole</b>						
PALOMA-1	165	R, OL, MC P: 29.6 months C: 27.9 months	High	Treatment naïve ER+/HER2- ABC	Primary: investigator assessed PFS Secondary: BICR PFS, OS; 1, 2, & 3-year survival; TTP; OR; CBR; DOR; AE; PROs	Not used
PALOMA-2	668	R, DB, MC 23 months	Low	Treatment naïve ER+/HER2- ABC	Primary: investigator assessed PFS Secondary: BICR PFS, OS; OR; DOR; DC/CBR; PROs; AE	Used in indirect comparison for cost- minimisation

AEs: Adverse events; ABC: Advanced breast cancer; BICR: Blinded Independent Central Review; CBR: Clinical benefit rate; DB: double blind; DC: Disease control; DOR: Duration of response; ER: oestrogen receptor; HER: epidermal growth factor receptor; HR: hormone receptor; MC: multi-centre; OL: open label; ORR: overall response rate; OR: objective response; OS: overall survival; PFS: progression-free survival; PROs: patient reported outcomes, R: randomised; TTP=Time to progression.

Source: compiled during the evaluation.

- 6.10 The next MONALEESA-2 interim analysis of OS is planned after approximately 300 deaths have been observed (late 2019), with a final analysis conducted after approximately 400 deaths observed (early 2020).
- 6.11 The data applied in the economic model were based on the January 2017 interim analysis. This is changed from the previous submission, which used data from the January 2016 and June 2016 interim analyses.
- 6.12 The PALOMA-2 outcomes are more robust for the indirect comparison with MONALEESA-2 due to the open-label nature of PALOMA-1.

### **Comparative effectiveness**

- 6.13 Figures 1 and 2 present the investigator assessed PFS and OS from the most recent analysis for the MONALEESA-2 trial. These figures are unchanged from the previous submission.

Figure 1: MONALEESA-2 Kaplan Meier Plot of PFS- Investigator assessed [REDACTED]

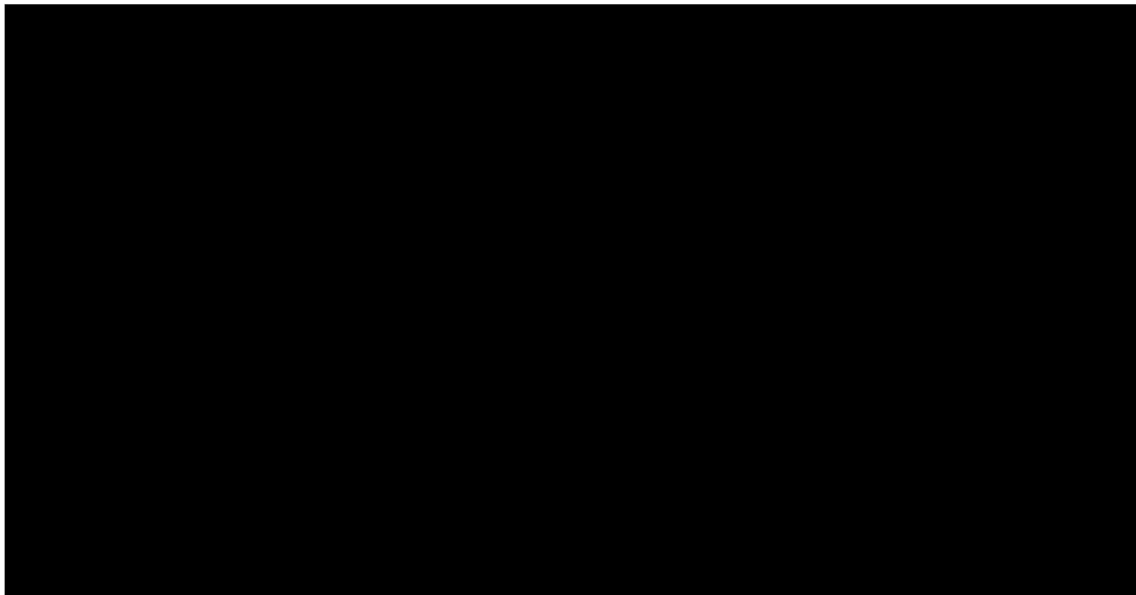


Figure 2: MONALEESA-2 Kaplan Meier plot of OS- Jan 2017



6.14 The key results from the MONALEESA-2 trial are presented in the table below. These results are unchanged compared to the previous submission.

Table 5: Results of PFS and OS in MONALEESA-2

MONALEESA-2 interim analysis	Ribociclib + Letrozole, n with event/N (%)	Letrozole, n with event/N (%)	Ribociclib + Letrozole, median months (95% CI)	Letrozole, median months (95% CI)	Difference, median months	HR (95% CI) <sup>a</sup>
<b>PFS</b>						
Investigator Jan 2016	93/334 (27.8)	150/334 (44.9)	NR	NR	NR	0.556 (0.429, 0.720) p-value <0.0001
BICR Jan 2016	NR	NR	NR	NR	NR	0.592 (0.412, 0.852) p-value 0.002
Investigator Jun 2016	118/334 (35.3)	179/334 (53.9)	22.4 (20.8, not estimable)	15.3 (13.4, 16.7)	7.1	0.559 (0.443, 0.706) p-value <0.0001
██████████ ██████████	██████████ ██████████	██████████	██████████	██████████	██████████	██████████ ██████████
<b>OS</b>						
Jan 2016	23/334 (6.9)	20/334 (6.0)	NR	NR	NR	1.128 (0.619, 2.055) p-value 0.653
Jun 2016	██████████	██████████	NR	NR	NR	NR
Jan 2017	50/334 (15.0)	66/334 (19.8)	NR	NR	NR	0.746 (0.517, 1.078) p-value 0.059

BICR: Blinded Independent Central Review; CI: confidence interval; NR: not reported, HR: Hazard Ratio; OS: overall survival; PFS: progression-free survival

<sup>a</sup> hazard ratio < 1 indicates a reduction in hazard rate in favour of ribociclib + letrozole.

Source: Table 2.14 p67, Table 2.15 p68, Table 2.16 p69, Table 2.17 p70, Table 2.18 p71, p68, p70 of the re-submission and calculated during the evaluation

- 6.15 Ribociclib resulted in a statistically significant improvement in PFS. The median difference in PFS was 9.3 months when investigator assessed. This result is unchanged from the previous submission.
- 6.16 At the January 2017 interim analysis, 15.0% of patients in the ribociclib + letrozole arm and 19.8% of patients in the letrozole alone arm had died. The difference in OS, although in favour of ribociclib (median increase not reached; 1.9/100 additional patients alive at 24 months), was not statistically significant (P=0.059). The PSCR (p2) reiterated the trend in favour of the ribociclib + letrozole arm, with a 25.4% risk reduction relative to placebo (HR 0.746; 95% CI: 0.517, 1.078). The ESC considered the immaturity of the OS data resulted in a high degree of uncertainty in the estimation of the magnitude of the long-term benefit. The pre-PBAC response (p1) noted the trial was designed to provide 90% power to detect a true OS HR of 0.72 at the time of the final analysis. At the time of the final OS analysis, approximately 400/668 or 60% of all patients in the MONALEESA-2 trial will have died, with an estimated mean duration of follow up of around five years.
- 6.17 For context, the PBAC recalled its previous considerations of treatment of HER2-positive breast cancer. As an example, the PBAC noted the incremental benefits in OS were statistically significant for pertuzumab + trastuzumab + docetaxel vs trastuzumab + docetaxel, at two different data cut-offs (May 2012 and February 2014, considered at the March 2014 and November 2014 meetings). The magnitude of the difference was larger than observed with palbociclib in PALOMA 1 (Table 6).

**Table 6: Benefits summary of pertuzumab (CLEOPATRA) and trastuzumab (M77001)**

Outcome	N	HRR or RR (95%CI)	Median months (95% CI)		Increment
			Pertuzumab + trastuzumab + docetaxel	Trastuzumab + docetaxel	
<b>Benefits</b>					
PFS (median months, 95% CI) (May 2012 cut-off)	808	0.69 (0.58, 0.81)	18.7 (17, 22)	12.4 (10, 14)	6.3
OS (median months, 95% CI) (May 2012 cut-off)	808	0.66 (0.52, 0.84)	Not reached (42, -)	37.6 (34, -)	N/A
OS (median months, 95% CI) (Feb 2014 cut-off)	808	0.68 (0.56, 0.84)	56.5	40.8	15.7

Source: Adapted from November 2014 Public Summary Document for item 7.5.

6.18 Details of the indirect comparison presented in the submission are provided in the table below.

**Table 7: Summary of results of the indirect comparison of PFS (ribociclib vs palbociclib)**

Trial type or estimate	Trial ID	n with event/N (%)	Letrozole alone n with event/N (%)	HR (95%CI)
Ribociclib + letrozole vs letrozole alone	MONALEESA-2, Jan 2017 Investigator assessed PFS	██████████	██████████	██████████
Palbociclib + letrozole vs letrozole alone	PALOMA-2, Feb 2016 Investigator assessed PFS	194/444 (43.7)	137/222 (61.7)	██████████
	BICR assessed PFS	152/444 (34.2)	96/222 (42.3)	
Indirect estimate of effect adjusted for the common reference <sup>a</sup>				██████████
Indirect estimate of effect adjusted for the common reference (using BICR assessed PFS) <sup>a</sup>				██████████

CI = confidence interval; n = number of participants with event; N = total number of participants in group; HR = hazard ratio; PFS = progression free survival

<sup>a</sup> hazard ratio < 1 indicates a reduction in hazard rate in favour of ribociclib + letrozole

Source: Table 2.16 p69, Table 2.35 p92 of the re-submission and Finn (2016) and PBAC (2017) Public Summary Document: Palbociclib

6.19 Based on the indirect comparison, there was no significant difference between ribociclib and palbociclib for PFS.

6.20 The re-submission did not present an updated indirect comparison based on OS results. Table below presents the results of an indirect comparison of OS conducted during the evaluation, based on MONALEESA-2 and PALOMA-1. An indirect comparison using PALOMA-2 was not possible because the OS hazard ratio has not been reported.

**Table 8: Summary of results of the indirect comparison of OS (ribociclib vs palbociclib)**

Trial type or estimate	Trial ID	n with event/N (%)	Letrozole alone n with event/N (%)	HR (95%CI)
Ribociclib + letrozole vs letrozole alone trials	MONALEESA-2 Jan 2017	██████████	██████████	██████████
Palbociclib + letrozole vs letrozole alone trials	PALOMA-1	30/84 (35.7)	31/81 (38.3)	██████████
Indirect estimate of effect adjusted for the common reference <sup>a</sup>				██████████

CI = confidence interval; n = number of participants with event; N = total number of participants in group; HR = hazard ratio; PFS = progression free survival

<sup>a</sup> hazard ratio < 1 indicates a reduction in hazard rate in favour of ribociclib + letrozole

Source: Table 2.18 p71 and PBAC (2017) Public Summary Document: Palbociclib

6.21 Based on the indirect comparison, there was no statistically significant difference between ribociclib and palbociclib for OS.

6.22 A limitation of the indirect analyses is the differences in baseline patient characteristics between the MONALEESA-2 and PALOMA-2 trials, and hence the results should be interpreted with caution.

### Comparative harms

6.23 The table below presents the incidence of adverse events (AEs) for the direct comparison of ribociclib + letrozole to letrozole alone using the MONALEESA-2 trial data. The re-submission provided additional data on the incidence of AEs based on the January 2017 interim analysis.

**Table 9: Summary of key adverse events in MONALEESA-2 (June 2016 interim analysis)**

Adverse events	Ribociclib + letrozole n with event/N (%)	Letrozole n with event/N (%)	RR (95% CI)
<b>June 2016 interim analysis</b>			
All AEs	██████████	██████████	██████████
Serious AEs	██████████	██████████	██████████
Grade ≥3 AE	██████████	██████████	██████████
Grade ≥3 AE requiring treatment	██████████	██████████	██████████
AEs leading to discontinuation	██████████	██████████	██████████
AEs requiring dose change/interruption	██████████	██████████	██████████
Deaths	██████████	██████████	██████████
On treatment deaths*	██████████	██████████	██████████
<b>January 2017 interim analysis</b>			
All AEs	██████████	██████████	██████████
Grade 3 AE	██████████	██████████	██████████
Grade 4 AE	██████████	██████████	██████████

AE: Adverse event; n: patients with event; N: total patients; RR: Relative risk.

\*Note: based on small patient numbers

Bold = statistically significant at 5% level

Source: Section 2 of the re-submission and calculated during the evaluation

6.24 Significantly more patients treated with ribociclib + letrozole compared with letrozole alone had AEs, serious AEs, Grade ≥3 AEs, Grade ≥3 AEs requiring treatment, AEs leading to treatment discontinuation and AEs requiring dose change/interruption. The largest differences between groups were for AEs leading to discontinuation and AEs requiring dose change/interruption (75.4% versus 17.0%).

6.25 In the MONALEESA-2 trial, based on the January 2017 interim analysis, the most commonly reported AEs with ribociclib + letrozole were neutropenia (██████████), nausea

(■■■%) and fatigue (■■■%). There were also reports of serious AEs, such as infections (grade 3 = ■■■% and grade 4 = ■■■%), febrile neutropenia (grade 3 = ■■■% and grade 4 = ■■■%), and pulmonary embolism (grade 3 = ■■■% and grade 4 = ■■■%).

- 6.26 The re-submission reported indirect comparisons of ribociclib + letrozole and palbociclib + letrozole in terms of Grade  $\geq 3$  AEs and discontinuation due to AE using the MONALEESA-2 trial (June 2016 interim analysis) and PALOMA-2 trial (February 2016 interim analysis). Ribociclib + letrozole was associated with a similar number of Grade  $\geq 3$  AEs, but a greater number of AEs leading to treatment discontinuation, compared with palbociclib + letrozole.

### ***Benefits and harms***

- 6.27 A summary of the comparative benefits and harms for ribociclib + letrozole versus letrozole alone is presented in the table below. The risk of harms is based on updated data compared to the previous submission.

Table 10: Summary of comparative benefits and harms for ribociclib + letrozole and letrozole alone

<b>Benefits</b>						
<b>PFS (investigator assessed): MONALEESA-2 (January 2017)*</b>						
Event	Ribociclib + letrozole		Letrozole alone		RD (%)	HR (95% CI)
Event free at 12 months, % (95%CI)	██████████		██████████		███	██████████
Event free at 24 months, % (95%CI)	██████████		██████████		███	██████████
<b>OS (investigator assessed): MONALEESA-2 (January 2017)*</b>						
Alive at 12 months, % (95%CI)	██████████		██████████		███	██████████
Alive at 24 months, % (95%CI)	██████████		██████████		███	██████████
<b>Harms</b>						
	Ribociclib + letrozole	Letrozole alone	RR (95% CI)	Events/100 patients*		RD (95% CI)
				Ribociclib + letrozole	Letrozole alone	
<b>Grade 3 adverse events</b>						
MONALEESA-2, Jan 2017	███	███	██████████	███	███	48 (42, 55)
<b>Grade 4 adverse events</b>						
MONALEESA-2, Jan 2017	███	███	██████████	███	███	15 (11, 19)
<b>Neutropenia</b>						
MONALEESA-2, Jan 2017	███	███	██████████	███	███	59 (54, 65)
<b>Grade 3 neutropenia</b>						
MONALEESA-2, Jan 2017	███	███	██████████	███	███	41 (35, 46)
<b>Grade 4 neutropenia</b>						
MONALEESA-2, Jan 2017	███	███	███	███	███	9 (6, 12)
<b>Nausea</b>						
MONALEESA-2, Jan 2017	███	███	██████████	███	███	23 (15, 30)
<b>Fatigue</b>						
MONALEESA-2, Jan 2017	███	███	██████████	███	███	9 (2, 16)
<b>Febrile neutropenia</b>						
MONALEESA-2, Jan 2017	███	███	███	███	███	1 (0, 2)

\* Median duration of follow-up 26.4 months (January 2017 interim analysis)

Abbreviations: HR = hazard ratio; NR: not reported; PFS: Progression-free survival; OS: Overall survival; RR = risk ratio.

Source: Compiled during the evaluation based on Table 2.28, p84 of the re-submission and Table 1-1 and 1-2, 4\_ML2\_2<sup>nd</sup> Int Anal\_OS\_Jan 2017.pdf and calculated during the evaluation.

6.28 On the basis of direct evidence presented by the re-submission, for every 100 patients treated with ribociclib plus letrozole in comparison to letrozole alone there would be:

- Approximately 12 more patients progression-free at 12 months, and 19 more patients at 24 months.
- No improvement in OS.
- Approximately 48 additional patients would experience a grade 3 adverse event and 14 would experience a grade 4 adverse event.
- Approximately 59 additional patients would experience neutropenia (low count of one type of white blood cell, neutrophils, which carries an increased risk of

infection), of which 41 would experience grade 3 neutropenia and 9 would experience grade 4 neutropenia.

- Approximately 23 additional patients would experience nausea.
- Approximately 9 additional patients would experience fatigue.
- Approximately 1 additional patient would experience febrile neutropenia (development of fever in a patient with neutropenia).
- The increased risk of pulmonary embolism (where an artery in the lungs becomes blocked by a blood clot) was small but observed in the clinical trial.
- The increased risk of occurrence of QTc interval prolongation (changes in the heart's rhythm) was small but observed in the clinical trial.

### ***Interpretation of the clinical evidence***

- 6.29 The submission claimed that ribociclib + letrozole provides superior efficacy and inferior safety compared with letrozole alone. This is unchanged from the previous submission.
- 6.30 The PBAC previously considered that the claim of superior efficacy was likely to be reasonable for PFS, however the immaturity of the OS data resulted in a high degree of uncertainty in the assessment of its magnitude of long-term benefit (PSD, July 2017, item 7.9). Given that the re-submission provided limited additional evidence of efficacy that addressed the PBAC concerns, the clinical claim of superior efficacy remains uncertain. The ESC considered that the benefit of ribociclib in delaying time to next therapy remains uncertain, in the context of other available therapies for advanced breast cancer including well-tolerated oral therapies. The pre-PBAC response (p1) reiterated the results from the MONALEESA trial for time to first subsequent anti-cancer therapy in which the median time (i.e. from randomisation to the first dose of post-study treatment) was 24.2 (95% CI: 20.9-27.6) months for ribociclib + letrozole versus 16.7 (95% CI 14.8-19.3) months for letrozole alone. It was noted in the pre-PBAC response that these results are consistent with those for PFS and indicate a statistically significant and clinically important difference and delay in accessing post progression treatment.
- 6.31 The PBAC previously considered that the claim of inferior safety is reasonable (PSD, July 2017, item 7.11). The additional data provided in the re-submission does not change this assessment. There is a high rate of AEs associated with ribociclib, with the majority of ribociclib + letrozole patients in the MONALEESA-2 trial experiencing Grade  $\geq 3$  AEs (█████%) and AEs leading to dose change or interruption (█████%). The ESC considered AEs could be managed by experienced clinicians. However, the ESC also noted the increased proportion of patients with prolongation of the QTc interval in the clinical trial. The ESC was concerned that occurrence of QTc interval prolongation and associated interactions with other medicines may be greater in the PBS population, given that patients were excluded from the clinical trial if they had cardiac risk factors, and while in the trial, were regularly monitored. The concerns about the cost of and who will perform the monitoring would also remain on PBS listing.
- 6.32 Overall, in the absence of a demonstrated gain in OS or quality of life, the ESC considered the benefits of ribociclib to be uncertain, and in this context noted the

UpToDate article by Hayes et al (last updated in August 2017), titled Systemic treatment for metastatic breast cancer: General principles, which states:

- The primary goals of systemic treatment for metastatic breast cancer are prolongation of survival, alleviation of symptoms, and maintenance or improvement in quality of life, despite toxicity associated with treatment.
- The optimal measure of therapeutic efficacy is debated. OS is the gold standard for comparing therapies, but it requires prolonged follow-up and may be diluted by the effects of subsequent treatment. However, no other endpoint, including progression-free survival, time to tumour progression, or objective response rate, has been shown to be a good surrogate for OS.

The pre-PBAC response (p1) argued that there is a substantive body of literature supporting the existence of what is a highly clinically plausible association, across the broader therapeutic area. The response also noted Hayes et al recognised the “consistent benefits observed with CDK inhibitors and AI” and “prefer(s) those regimens in the front-line setting”.

- 6.33 The submission claimed that ribociclib + letrozole provides similar effectiveness and safety to the alternative near market comparator, palbociclib + letrozole. This is changed from the previous submission, which claimed that “Ribociclib + letrozole provides non-inferior effectiveness and safety to the alternative near market comparator, palbociclib + letrozole”.
- 6.34 The PBAC previously considered that the indirect comparison against palbociclib presented in the submission did not demonstrate a significant difference in PFS. However, the PBAC considered that lack of evidence of a significant difference is not equivalent to evidence of no difference (non-inferiority). Furthermore, there was limited exchangeability across MONALEESA-1 (ribociclib) and PALOMA-1 and PALOMA-2 (palbociclib) trials. The PBAC also noted that there were significantly more treatment discontinuations resulting from AEs for ribociclib plus letrozole compared with palbociclib plus letrozole. Overall, the PBAC advised that there was limited data to support the submission’s claim of non-inferiority in effectiveness and safety compared with palbociclib (PSD, July 2017, item 7.12).
- 6.35 Despite the re-submission updating the indirect comparison to use data from the most recent MONALEESA-2 interim analysis (January 2017), many of the issues previously identified by the PBAC still remain.
- 6.36 The PSCR noted that the open label PALOMA-1 trial was excluded from the indirect comparisons and argued that MONALEESA-2 and PALOMA-2 trial had reasonable exchangeability in terms of compatible design, broadly consistent eligibility criteria, identical co-administration and comparator treatment regimens, similar outcomes, similar methods of statistical analysis, similar treatment settings, and conducted within a largely overlapping time period. The PSCR also noted that the event rates were similar at comparable follow-up durations in the trials. The ESC noted the limitations of the indirect comparison, but agreed with the PSCR that it is likely that the two agents would provide similar effectiveness in terms of the key patient relevant outcomes of PFS and overall response rate (ORR). The pre-PBAC response stated this approach will help to ensure that patients and clinicians have a choice

between the two medicines in the PBS setting, which may be important given potential differences in tolerability, presentation and convenience.

6.37 The ESC noted there is a difference in the safety profile of palbociclib and ribociclib. The magnitude of events is similar however the type of adverse events differs. The discontinuations rates in the trials of the agents were different. This may lead to clinicians choosing a particular agent (palbociclib vs ribociclib) based on safety profile.

6.38 The pre-PBAC response drew the Committee’s attention to

These elements were claimed to enhance clinician confidence in managing the treatment of patients with ribociclib, so as to minimise the impact of adverse events and maximise outcomes.

### **Economic analysis**

6.39 The submission presented a cost-effectiveness and cost-utility analysis comparing ribociclib + letrozole and letrozole alone, based on the MONALEESA-2 trial as well as external data sources and implementing a modelled evaluation.

**Table 11: Summary of model structure and rationale.**

<b>Component</b>	<b>Summary</b>
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Outcomes	PFS, OS, QALYs and LYs
Time horizon	10 years in the model base case vs 26.4 months (median) in the MONALEESA-2 trial (January 2017), which is ongoing. The time horizon is unchanged from the previous submission. Previously, the PBAC considered that a time horizon no more than 5 years would be appropriate, given the immaturity of the existing survival data and resulting uncertainties surrounding a potential OS benefit (PSD, July 2017, item 4.14).
Methods used to generate results	Partitioned survival model. This is unchanged from the previous submission.
Health states	<ul style="list-style-type: none"> <li>• Pre-progression:                             <ul style="list-style-type: none"> <li>- In both treatment groups, this is further partitioned by response status (ORR vs SD)</li> <li>- Within the RIB+LTZ group only, this is further partitioned by continued ribociclib treatment status (on vs off)</li> </ul> </li> <li>• Post-progression</li> </ul> Dead Two errors were identified in the updated model in terms of: 1) estimating the life years gained, and 2) estimating the time in the ORR and SD states.
Utilities	EQ-5D-5L (UK tariff) from MONALEESA-2 (January 2017) analysed using a mixed-effects model. Utilities estimated for ORR, SD and progressive disease. No difference by treatment. This is changed from the previous submission, which used data from the January 2016 interim analysis.  The utility value in the Post-progression health state was largely driven by a single end of treatment visit. Consequently, the utility value for the Post-Progression health state is likely to be over-estimated (higher than expected over the long term), compared to if utility values were measured throughout the Post-Progression health state. <i>This is likely to favour ribociclib.</i>  Disutilities associated with AEs, based on the incidence of grade $\geq 3$ AEs and Hudgens (2016). Assumed grade 3 AE duration is 14 days, and grade 4 AE duration is 28 days. The general approach is unchanged

Component	Summary
	<p>from the previous submission, however additional disutilities were applied in the model (diarrhoea, anaemia and infections). The estimated disutilities were not reported in the abstract provided by the submission, and so the results were unable to be verified. The duration of some AEs may be underestimated, especially fatigue.</p>
Cycle length	<p>1 month (30.44 days)</p>
Survival rates	<p>ORR was based on the MONALEESA-2 trial (January 2017, investigator assessed). Varies over time. This is changed from the previous submission, which used data from the June 2016 interim analysis and did not vary ORR over time.</p> <p>PFS and OS were used to quantify the proportions of patients in the Pre-progression and Dead health states, respectively. A more appropriate approach is to estimate post-progression survival using patient-level data from the MONALEESA-2 trial.</p> <p>PFS: For first 25 months used MONALEESA-2 investigator-assessed PFS (Kaplan-Meier) data (January 2017). Extrapolated using fitted Weibull functions. This is changed from the previous submission, which was based on data from the January 2016 interim analysis and extrapolated using fitted lognormal functions.</p> <p>OS: For first 25 months used MONALEESA-2 OS (Kaplan-Meier) data (January 2017). Extrapolated using fitted Weibull functions. This is changed from the previous submission, which was based on external data sources.</p> <p>TTD, ribociclib + letrozole: For first 25 months used MONALEESA-2 TTD (Kaplan-Meier) data (January 2017). Extrapolated using a fitted Weibull function. This is changed from the previous submission, which was based on data (date unknown) and extrapolated using a fitted exponential function.</p> <p>TTD, letrozole alone: assumed to be equal to PFS. This is unchanged from the previous submission.</p> <p>Regarding PFS, OS and TTD, the results were unable to be verified as the re-submission did not provide any patient level data, programming code or output logs.</p> <p>The choice of extrapolation functions are uncertain as: 1) whether an assumption of proportional hazards would be appropriate was not explored (in the case of PFS and OS); 2) there was limited difference in the estimates of goodness-of-fit (AIC and BIC) for the different functional forms; 3) the observed data used to fit the parametric function was limited relative to the time horizon of the model; and 4) the extrapolation functions diverge from the observed Kaplan-Meier data in later months.</p> <p>In the case of PFS and OS, the re-submission assumed that the treatment effect persists for the model duration. This is not appropriate, especially given that the difference in OS in MONALEESA-2 was not statistically significant, and the duration of follow-up in the trial relative to the time horizon in the model.</p>
Costs	<p><u>The re-submission considered drug acquisition costs, the cost of monitoring patients and managing clinically relevant AEs, post-progression anti-cancer therapy (PPACT) costs, and other costs associated with treatment.</u></p> <p><u>Drug acquisition costs</u></p> <p>For first 25 months used the observed number of patients receiving each dose level (600/400 200 mg/day) of ribociclib each month in MONALEESA-2 to estimate the proportion of patients receiving each dose level. From month 26 onwards, the proportions were assumed to remain constant. The duration of treatment based on TTD. The approach to estimating the dose of ribociclib received has changed from the previous submission, which applied an RDI of █████% to the pack size 63 x 200mg. The updated approach is reasonable. The prices of letrozole and anastrozole will be reduced on 1 October 2017 due to price disclosure.</p> <p><u>PPACT</u></p> <p>The re-submission included one-off costs of PPACT. This is changed from the previous submission, which excluded these costs. Note that these costs do not change with the length of time in the post-progression state, and so do not address the issue that longer OS will result in larger total treatment costs.</p> <p>The re-submission assumed that PPACT consisted of everolimus + exemestane (second line, █████% of</p>

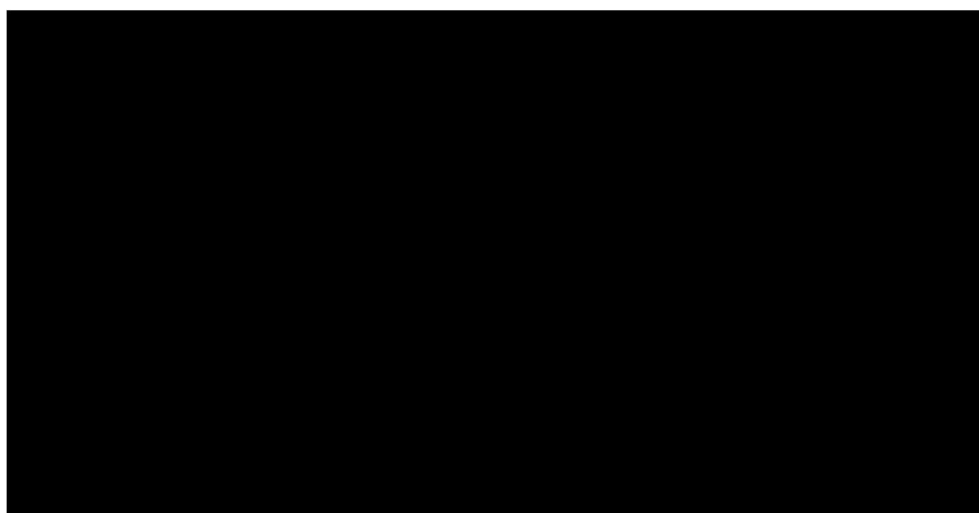
Component	Summary
	patients) followed by capecitabine (third line, █% of patients) (p133 of the re-submission). This is uncertain – patients may also receive nab-paclitaxel, vinorelbine, peg-liposomal doxorubicin, doxorubicin, or cyclophosphamide + doxorubicin. The average treatment duration with was based on published sources. This is reasonable. The re-submission did not include the cost of IV administration or any ancillary drugs.

ABC: Advanced breast cancer; AE: Adverse event; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; CT: Computed tomography; ECG: electrocardiograph; EUC: serum electrolytes; FBC: full blood count; LFT: liver function tests; LYs: Life years; MRI: Magnetic resonance imaging; ORR: Overall response rate; OS: Overall survival. PFS: Progression free survival; PPACT: post-progression anti-cancer therapy; QALY: Quality adjusted life year; SD: Stable disease; TTD: Time to treatment discontinuation.

Source: Table 3.1, p101 of the re-submission and compiled during the evaluation

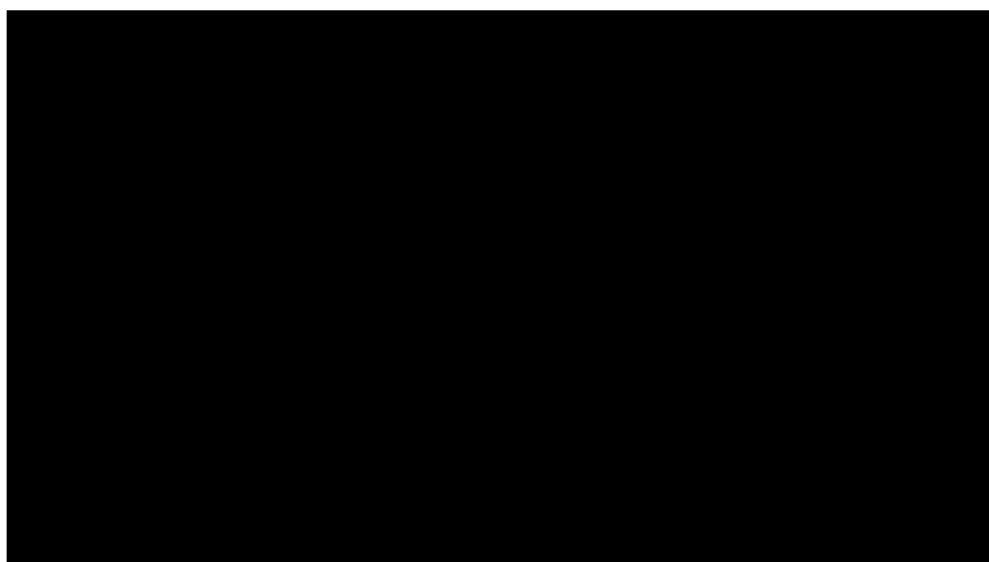
6.40 Figure 3 and Figure 4 show the extrapolation of PFS and OS in the letrozole alone and ribociclib + letrozole groups based on the Weibull function fitted to data obtained from the MONALEESA-2 trial.

**Figure 3: Model trace for PFS for ribociclib + letrozole versus letrozole alone (Weibull extrapolation)**



Source: Table 3.14, p134

**Figure 4: Model trace for OS for ribociclib + letrozole versus letrozole alone (Weibull extrapolation)**



Source: Table 3.14, p134

6.41 The key drivers of the model are provided in table below.

**Table 12: Key drivers of the model**

Description	Method/Value	Impact
Time horizon	10 years; extrapolated from 26 months.	High, favours ribociclib
Extrapolation of OS	Weibull, extrapolated from 26 months. Compared to any other parametric function.	High, favours ribociclib
Utility post-progression	MONALEESA-2 in the base case. Compared to a applying a decrement for progression from Lloyd (2016) (██████████).	Moderate, favours ribociclib

Source: compiled during the evaluation

6.42 Results of the economic evaluation are provided in the table below. A stepped analysis was not presented in the re-submission. This table also includes the results of the economic evaluation included in the July 2017 submission.

**Table 13: Results of the economic evaluation**

	Ribociclib +letrozole	Letrozole	Increment
Costs	\$██████████	\$██████████	\$██████████
LYs	██████████	██████████	██████████
QALYs	██████████	██████████	██████████
Incremental cost/extra LY gained			\$██████████
Incremental cost/extra QALY gained			\$██████████
<b>Results of the economic evaluation – errors fixed</b>			
Costs	\$██████████	\$██████████	\$██████████
LYs	██████████	██████████	██████████
QALYs	██████████	██████████	██████████
Incremental cost/extra LY gained			\$██████████
Incremental cost/extra QALY gained			\$██████████
<b>July 2017 submission</b>			
Results of the economic evaluation – July 2017 submission			
Costs	\$██████████	\$██████████	\$██████████
LYs	██████████	██████████	██████████
QALYs	██████████	██████████	██████████
Incremental cost/extra LY gained – July 2017			\$██████████
Incremental cost/extra QALY gained – July 2017			\$██████████

LY: Life years; QALYs: quality adjusted life years. Source: Table 3.A.8.4 of the re-submission and Table 3.32 (p. 144) of the previous submission

The redacted table shows ICERs in the range of \$45,000/QALY - \$200,000/QALY.

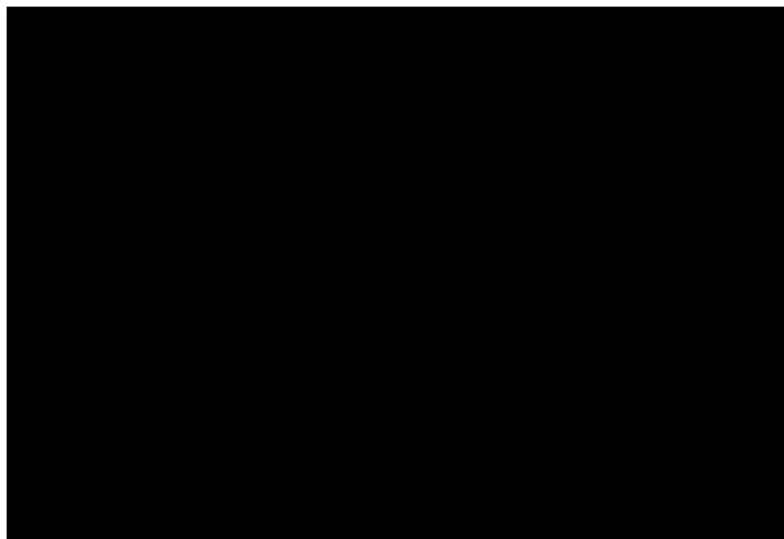
6.43 During the evaluation the following issues were identified with the analysis:

- A time horizon of 10 years was applied in the economic model. The economic model projected a significant improvement in median OS of █████ months and mean (undiscounted) life years gained of █████ years (████ months) (with an error in the model fixed) over 10 years. The ESC considered that this gain in life years was overly optimistic and highly uncertain, given there is only 26.4 months (median) of follow-up in the MONALEESA-2 trial (January 2017), the median difference in OS in the trial is currently unknown, and the difference was not statistically significant (P=████). The sponsor has proposed to address this uncertainty through a Managed Entry Scheme (MES, also known as Managed Access Program, see Financial management –

risk sharing arrangements below). Previously, the PBAC considered that a time horizon no more than 5 years would be appropriate, given the immaturity of the existing survival data and resulting uncertainties surrounding a potential OS benefit (PSD, July 2017, item 4.14). The PSCR (p3) argued that the nominated time horizon of 10 years represents a trade-off between the duration of follow up in the MONALEESA-2 trial and the likely (lifetime) period over which incremental costs and outcomes are expected to accrue in the Australian treatment setting. It was further argued, based on predicted survival outcomes, a true lifetime perspective for ribociclib would require a time horizon of more than 20 years. The PSCR disagreed with the use of a 5 year time horizon. The ESC considered that the re-submission had not addressed the previous view of the PBAC that a shorter time horizon was appropriate given the immaturity and uncertainty of the existing OS data. The pre-PBAC response argued that artificially truncating the time horizon of the analysis at 5 years represents a very blunt approach to managing the uncertainty inherent in circumstances where available randomised controlled trial data are relatively immature, but likely durations of treatment and incremental clinical effectiveness are long. The sponsor considered that it would be more appropriate to address this uncertainty via a MES based on currently maturing OS data.

- The re-submission assumed that the treatment effect persists for the model duration. The PSCR (p3) disagreed with the perspective that this is not appropriate. The ESC considered that this assumption was overly optimistic, given the immaturity of the existing OS data and subsequent uncertainties surrounding the potential OS benefit. The ESC questioned the biological plausibility of this assumption. The pre-PBAC response stated that the sponsor does not believe it is biologically implausible that this would be maintained well beyond the time horizon of the trial. The primary effect of ribociclib, which has been clearly demonstrated in the MONALEESA-2 trial, is to delay disease progression. In the absence of a post-treatment rebound effect, for which there is currently no evidence, this will very plausibly lead to a permanent shift to the right in OS outcomes.
- The application of Weibull functions to extrapolate OS is uncertain as: 1) whether an assumption of proportional hazards would be appropriate was not explored; 2) there was limited difference in the estimates of goodness-of-fit (AIC and BIC) for the different functional forms; 3) the observed data used to fit the parametric function was limited relative to the time horizon of the model; and 4) the extrapolation functions diverge from the observed Kaplan-Meier data in later months. The ESC noted that the approach in the re-submission for extrapolating outcomes was more appropriate than the approach used in the July 2017 submission. The ESC noted the comparison of OS traces with different extrapolation functional forms which show the uncertainty of the size of the extrapolated benefit due to limited OS data (see Figure 5). The ESC noted that the cost/QALY is relatively sensitive to choice of functional form for extrapolation of the OS, but less sensitive to the choice of functional form for extrapolation of the PFS.

**Figure 5: Model trace for OS for ribociclib + letrozole alone with different functional forms**  
(observed KM data in black bold). (letrozole alone, not included in the graph)



Constructed during the evaluation

- The utility value in the Post-Progression state was largely driven by a single end of treatment visit. Consequently, the utility value for the Post-Progression state is likely to be over-estimated, compared to if utility values were measured throughout the Post-Progression state. While the ESC agreed with the evaluation on the effect of the approach, it also agreed with the PSCR (p5) that the impact of changing this assumption on the cost/QALY gained was likely to be modest.
  - The cost of post-progression anti-cancer therapy (PPACT) did not vary with time in the post-progression state, a limited range of chemotherapies were considered (in particular, nab-paclitaxel was not considered as a potential line of therapy), and the cost of IV administration and ancillary drugs for PPACT were not included. The PSCR (p4) provided further information (Blackwell et al, 2017) on the patterns of PPACT use based on the January 2017 interim analysis of the trial to support the approach adopted in the re-submission.
- 6.44 The table below shows the results of key uncertainty analyses. The error regarding the estimation of overall response rate (ORR) and stable disease (SD) in the model was not fixed in this table as it made a minimal impact on the cost/QALY gained.

**Table 14: Results of scenario and univariate sensitivity analyses**

Scenario analyses					
Analysis	Base Case	Scenario 1		Scenario 2	
	Value	Value	Cost/QALY	Value	Cost/QALY
Base case = \$ [REDACTED]					
OS parametric model	Weibull	Exponential	\$ [REDACTED]	Log-logistic	\$ [REDACTED]
Utility weights data source	MONALEESA-2	Lloyd	\$ [REDACTED]	Shiroiwa	\$ [REDACTED]
Utility values in Post-Progression state	MONALEESA-2	Lloyd (2016) decrement	\$ [REDACTED]	NA	
One way sensitivity analyses					
Analysis	Base Case	Worst case		Best case	
	Value	Value	Cost/QALY	Value	Cost/QALY
Time horizon	10 years	5 years	\$ [REDACTED]	20 years	\$ [REDACTED]

AE: adverse event; DPMQ: dispensed price for maximum quantity; LTZ: letrozole; ORR: overall response rate; OS: overall survival; PPACT: post-progression anti-cancer therapy; RIB: ribociclib; TTD: Time to deterioration in ECOG performance status.  
Source: Table 3.33 p142 of the re-submission

The redacted table shows ICERs in the range of \$45,000/QALY - \$200,000/QALY.

- 6.45 The model was most sensitive to time horizon, followed by the parametric function applied to extrapolate OS. Applying any extrapolation function other than the Weibull function increased the ICER. The model was also sensitive to the utility values applied in the post-progression state.
- 6.46 Sensitivity analyses on the shape and scale parameters describing the parametric function were not conducted. These were unable to be conducted during the evaluation as the upper and lower 95% confidence intervals were not reported by the re-submission and output logs were not provided.
- 6.47 Overall, the ESC considered that the base case cost/QALY in the re-submission was underestimated.
- 6.48 The submission also presented a cost-minimisation analysis comparing ribociclib + letrozole and palbociclib + letrozole. The estimation of equi-effective doses were based on mean relative dose intensity (RDI) and regimen intensity of 21 days in each 28-day cycle. The re-submission calculated the equi-effective doses to be ribociclib [REDACTED] mg (600 mg x [REDACTED]% RDI [mean from MONALEESA-2 trial] x 21/28 days) and palbociclib 87.19 mg (125 mg x 93.0% RDI [median from PALOMA-2 trial] x 21/28 days).
- 6.49 The re-submission reduced the RDI applied to ribociclib from [REDACTED]% (based on the mean RDI in the January 2016 interim analysis of the MONALEESA-2 trial) to [REDACTED]% (based on the mean RDI in the January 2017 interim analysis of the MONALEESA-2 trial. The pre-PBAC response stated the median RDI from the published interim analysis (93%) was used for palbociclib as a mean value was not publically available. The sponsor acknowledged commercial-in-confidence data shared by the sponsor of palbociclib may be used to inform the equi-effective doses.
- 6.50 The PBAC previously considered that the lower RDI for ribociclib is inconsistent with the claim of non-inferior safety between ribociclib + letrozole and palbociclib plus letrozole. It also results in the price for ribociclib being higher than if the same RDI

was applied to ribociclib and palbociclib (PSD, July 2017, item 6.43). The PSCR (p4) and pre-PBAC response (p3) strongly disagreed with this perspective and argued that the average cost per day based on the average dose of the respective treatment regimens in the cost minimisation is identical, however, given the different presentations of the two medicines, this translates into different costs per pack, with ribociclib offering a pack configuration that may lead to less wastage when a dose change/reduction is indicated.

6.51 No additional costs or offsets were included in the cost-minimisation analysis.

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

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

6.52 The drug cost per patient per year was based on a cost of \$ [REDACTED] for 63 tablets x 200mg, \$ [REDACTED] for 42 tablets x 200mg and \$ [REDACTED] for 21 tablets x 200mg, assuming a full year of treatment (12 months) and inclusive of dose adjustments (based on data on the dose received from the MONALEESA-2 trial). The submission did not include the cost of letrozole in this estimate.

6.53 This is changed from the previous submission which estimated a cost per patient per year of \$ [REDACTED] for ribociclib + letrozole. This was based on a cost of \$ [REDACTED] for 63 tablets x 200mg, assuming a full year of treatment, and inclusive of dose adjustments (RDI = [REDACTED]%).

6.54 Based on the economic model, the undiscounted total cost of ribociclib per patient is \$ [REDACTED]. The pre-PBAC response stated that this is based on a modelled mean duration of treatment of around [REDACTED] years.

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

6.55 This submission was not considered by DUSC.

6.56 The submission used an epidemiological (prevalence based) approach with the number of post-menopausal, HR+/HER2- ABC patients currently on first line hormonal therapy, which was estimated from the IPSOS Australian Oncology Monitor. The submission assumed [REDACTED]% growth of ribociclib use over six years based on historical letrozole prescription growth from Medicare Australia prescribing data, and [REDACTED]% treated with 200mg dose, [REDACTED]% treated with 400mg dose, and [REDACTED]% treated with 600mg dose based on the MONALEESA-2 trial.

6.57 The total net financial cost for the Australian Government was estimated to be more than \$100 million over 6 years.

**Table 15: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Eligible and suitable patients						
Number of patients treated						
Number of scripts dispensed (PBS/RPBS) <sup>a</sup>						
Ribociclib 21 tab packs						
Ribociclib 42 tab packs						
Ribociclib 63 tab packs						
<b>Estimated financial implications of ribociclib</b>						
Cost to PBS/RPBS						
Copayments						
Cost to PBS/RPBS less copayments						
<b>Estimated financial implications for tamoxifen, letrozole, anastrozole, and exemestane</b>						
Cost to PBS/RPBS						
Copayments						
Cost to PBS/RPBS less copayments						
<b>Net financial implications</b>						
Net cost to PBS/RPBS						
Net cost to MBS						
Net cost to Australian Government						
<b>July 2017 submission</b>						
Number of patients treated						
Estimated financial implications of ribociclib, Cost to PBS/RPBS less copayments						
Net cost to PBS/RPBS						
Net cost to MBS						
Net cost to Australian Government						

<sup>a</sup> Assuming 13.04 scripts per year as estimated by the re-submission.

Source: Table 4.7 and 4.8 p153-4, 4.12 p157 of the re-submission and Section 4 Workbook.xlsx, Sheet 4c. Displaced - EFF

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be more than \$100 million per year.

6.58 Issues identified during the evaluation are as follows:

- The number of patients with breast cancer and the proportion with Stage IIIb/c or Stage IV may be under-estimated. The PSCR (p5) argued that the prevalent Stage IIIb/c or Stage IV population is likely to contribute a smaller proportion of the overall prevalent BC population compared with the incident population of

advanced disease due to shorter duration of survival than the overall breast cancer population. The ESC considered this to be a reasonable argument.

- The estimated market share (up to █%) was based on expert opinion and is highly uncertain. Uptake may be shared between palbociclib and ribociclib if palbociclib, a near market comparator, is also concurrently PBS-listed. The re-submission reduced uptake to █% in every year in the July 2017 submission. The ESC considered given the community's interest in this oral treatment that the early years' estimate of uptake, particularly in year 1, was underestimated. The pre-PBAC response (p3) explained that the choice of █% was informed by IPSOS data suggesting that this is the rate of the current prevalent, eligible population diagnosed as advanced each year.
- The dose intensity in practice may differ to that observed in the clinical trial.
- Some clinicians may continue to treat patients with ribociclib (or a NSAID) after progression, despite the approach used in the clinical trials. The PSCR (p5) argued that clinicians will not continue to treat patients with ribociclib after progression due to the inclusion of RECIST criteria in the proposed PBS restriction and there are several treatment options available for patients who may progress on ribociclib. The ESC, now that there is more clinic experience using CDK4/6 inhibitors, agreed with the PSCR (p3) that it is not likely that patients would be treated beyond progression.
- The ESC considered the uncertainty with the average treatment duration (as noted for the economic model) also impacts on the estimated financial impact of the listing. The pre-PBAC response argued that this uncertainty should be reflected in the estimated change in the prevalent population and not the number of packs per patient per calendar year.
- Additional medicine costs to treat adverse events associated with ribociclib were not included. The PSCR (p5) clarified that the re-submission included MBS items used to monitor patients and treat Grade 3 AEs were included and most AEs are managed with dose modifications.
- The DPMQ of letrozole will be reduced by 22.65% and anastrozole will be reduced by 12.60% on 1 October 2017 due to price disclosure arrangements.
- The TGA Delegate's Overview noted that "█" (p3 of the TGA Delegates Overview). The number of monitoring tests may be underestimated. As discussed above, the ESC noted there would be costs associated with monitoring related to the risk of QTc interval prolongation. The pre-PBAC response stated there is no increase in required QTc monitoring in the TGA approved PI from that proposed in the re-submission. █.

### **Quality use of medicines**

- 6.59 The re-submission did not raise any potential concerns regarding the quality use of medicines. This is unchanged from the previous submission.
- 6.60 Considering ribociclib is potentially a first in class medication and its use is associated with high rates of serious AEs, a plan to ensure the appropriate use of ribociclib, monitoring regimens and managing AEs should have been included. This includes support towards healthcare professionals (both in primary and secondary settings), community pharmacy (if listed as Section 85), and patients.

### **Financial management – risk sharing arrangements**

- 6.61 The re-submission did not propose a particular risk sharing arrangement. Instead, it presented a proposed [REDACTED]. The proposal had two options for a potential framework for a “[REDACTED]” scheme to address the key issue of lack of mature overall survival data (and hence lack of certainty of the magnitude of the incremental benefit in terms of QALYs gained) for ribociclib (and the CDK4/6 class of drugs) over letrozole or anastrozole used in the treatment of breast cancer. While both options would require a re-evaluation of the modelled incremental cost-effectiveness ratio at a later time point, [REDACTED].

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of ribociclib on the PBS in combination with a non-steroidal aromatase inhibitor (NSAI) for first-line endocrine based treatment of patients with non-premenopausal, hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC) on the basis of high and uncertain cost effectiveness, and uncertainties regarding the magnitude of incremental benefit of ribociclib. Additionally, the PBAC considered that the likely net cost of listing ribociclib on the PBS, though less than proposed in the July 2017 submission, represented a significant opportunity cost to the Commonwealth.
- 7.2 The PBAC recalled that this re-submission was lodged for consideration before the sponsor had the PBAC minutes for the July 2017 meeting and that the PSCR was the first opportunity that the sponsor had to directly address the PBAC’s concerns. The PBAC noted that re-submission and subsequent responses had not addressed all of the PBAC’s concerns of the July 2017 submission.
- 7.3 The PBAC noted the consumer comments and acknowledged there is significant public interest in the listing of ribociclib. The consumer comments noted that ribociclib could help improve breast cancer patients’ quality of life but there is currently a high financial cost.
- 7.4 The PBAC recalled that there is a strong clinical benefit of endocrine-based therapy alone as first-line therapy in many patients, and a number of effective and well-

tolerated second-line therapies (including oral treatments) are currently available for patients who progress after first-line endocrine-based therapy.

- 7.5 The PBAC noted that the proposed restriction was aligned better with the inclusion criteria of the MONALEESA-2 trial, compared with that considered in July 2017. However, if both listed on the PBS, the PBAC considered ribociclib and palbociclib should have similar restriction criteria given they belong to the same class of drug and are registered for similar indications. The PBAC recommended that any points of difference, such as clinical criteria for access, would need to be clearly justified and defined. Further, the PBAC recalled that it had recommended a restricted benefit listing for goserelin 3.6 mg implant for anticipated premature ovarian failure for patients receiving treatment with an alkylating agent for a malignancy or an autoimmune disorder that has a high risk of causing premature ovarian failure. This listing may impact on some criteria proposed for the listing of ribociclib.
- 7.6 The PBAC noted that re-submission requested an initial grandfather restriction to cover those patients who are currently receiving ribociclib + letrozole [REDACTED] and patients who have received  $\leq 28$  days of treatment with a NSAI via the PBS, and that the proposed restriction was broader than the restriction proposed for initiating treatment. The PBAC considered that the requirement of, and criteria for, a grandfather restriction would need to be considered in a resubmission for ribociclib.
- 7.7 The PBAC considered that the nominated main comparator, a NSAI (i.e. letrozole or anastrozole) alone, remained appropriate. The PBAC considered that palbociclib was an appropriate near market comparator, and noted palbociclib was also considered by the Committee for a similar indication at its November 2017 meeting.
- 7.8 The PBAC noted the re-submission was based on the same head-to-head phase III, randomised, double-blind trial comparing ribociclib + letrozole to letrozole alone in postmenopausal women with HR+, HER2- ABC (MONALEESA-2) as presented in the original submission. The re-submission presented limited additional evidence of efficacy and the PBAC's previous concerns regarding the clinical claim of superior efficacy being uncertain remained. The PBAC previously considered that the claim of superior efficacy based on PFS was likely to be reasonable; ribociclib resulted in a statistically significant improvement in PFS with a median increase of 9.3 months when investigator assessed. The difference in OS, although in favour of ribociclib, remained not statistically significant ( $p=0.059$ ). Due to the immaturity of the OS data, the high degree of uncertainty in the magnitude of long-term benefit with ribociclib remained. The PBAC noted the final OS analysis is unlikely to be available until 2020.
- 7.9 The PBAC previously considered that the claim of inferior safety to be reasonable, and noted that the additional data provided in the re-submission did not change this assessment. The PBAC noted the high rate of adverse events (AEs) associated with ribociclib, with the majority of ribociclib + letrozole patients in the MONALEESA-2 trial experiencing Grade  $\geq 3$  AEs (83.6%) and AEs leading to dose change or interruption (75.4%). The PBAC also noted the increased proportion of patients with prolongation of the QTc interval in the clinical trial. The PBAC agreed with the ESC that occurrence of QTc interval prolongation and associated interactions with other medicines may be greater in the PBS population, given that patients were excluded

from the clinical trial if they had cardiac risk factors, and while in the trial, were regularly monitored.

- 7.10 The PBAC noted the updated analyses presented in the re-submission and performed during the evaluation for the indirect comparison against palbociclib. Based on the indirect comparison of PFS using the MONALEESA (ribociclib) and PALOMA-2 (palbociclib) trials, the PBAC considered it is reasonable to conclude that the two agents are non-inferior. The PBAC considered that there were insufficient OS data for both ribociclib and palbociclib to enable a meaningful comparison based on this outcome. The PBAC recalled that there were significantly more treatment discontinuations resulting from AEs for ribociclib plus letrozole compared with palbociclib plus letrozole, while the number of Grade  $\geq 3$  AEs was similar. The PBAC advised that the indirect comparison should be updated in any re-submission in the event that further follow-up data are available for either ribociclib or palbociclib.
- 7.11 The PBAC noted the equi-effective doses proposed in the re-submission, and the sponsor's acknowledgement that committee-in-confidence data may be used to inform the dose of palbociclib. The PBAC advised that the equi-effective doses should be based on the most complete dosing data available for ribociclib and palbociclib.
- 7.12 For the comparison versus letrozole alone, the PBAC agreed with the ESC that the base case cost/QALY of \$45,000 - \$75,000 presented in the re-submission was substantially underestimated. The PBAC noted the following issues with the economic model:
- The model estimated an increase in median OS of ■ months and a mean (undiscounted) gain of ■ life years (■ months) over the 10 year time horizon. The PBAC agreed with ESC and considered that this gain in life years was overly optimistic and highly uncertain, given there is only 26.4 months (median) of follow-up in MONALEESA-2 (January 2017), the median difference in OS in the trial is currently unknown, and the difference was not statistically significant ( $P=0.059$ ).
  - The 10 year model time horizon was unchanged from the previous submission. The PBAC recalled that it had previously considered that a time horizon no more than 5 years would be appropriate. Using a 5 year time horizon increased the incremental cost-effectiveness ratio (ICER) from a base case of \$45,000/QALY - \$75,000/QALY to \$105,000/QALY - \$200,000/QALY. Noting the arguments in the sponsor's PSCR and pre-PBAC response, the PBAC reiterated its view that a shorter time horizon was appropriate given the immaturity of the existing OS data and that any increase in OS was uncertain at the moment.
  - The re-submission assumed that the treatment effect persists for the model duration. The PBAC agreed with the ESC and considered that this assumption was overly optimistic, given the immaturity of the existing OS data and subsequent uncertainties surrounding the potential OS benefit.
  - The PBAC noted a Weibull function was applied to extrapolate OS. Sensitivity analysis found that the application of any extrapolation function other than the Weibull function increased the ICER (from \$75,000/QALY - \$105,000/QALY gained (log-logistic) to QALY\$105,000/QALY - \$200,000/QALY gained (exponential)). The

PBAC agreed with the ESC and considered that the approach in the re-submission for extrapolating outcomes was more appropriate than the approach used in the July 2017 submission. However, the PBAC noted the comparison of OS traces with different extrapolation functional forms shows the uncertainty of the size of the extrapolated benefit due to limited OS data (see Figure 5). The PBAC noted that the cost/QALY is relatively sensitive to choice of functional form for extrapolation of the OS, but less sensitive to the choice of functional form for extrapolation of the PFS.

- The PBAC noted ESC's comments regarding the post-progression utility value largely being driven by a single end of treatment visit, although noted based on the current model structure and inputs, that the impact of changing this value on the cost/QALY was small in comparison to the impact of changing parameters associated with estimating the OS gain.
- 7.13 The resubmission estimated the total net financial impact to the Australian Government of listing ribociclib was more than \$100 million over the next 6 years. The PBAC considered that this is likely to be an underestimate given the issues raised in the evaluation and by the ESC.
- 7.14 The PBAC noted that there remained a significant opportunity cost of listing ribociclib, particularly in the context of the uncertainty of cost-effectiveness driven by immature survival data. In this regard, the PBAC reiterated that a risk share agreement that appropriately limits the financial risk to the Commonwealth would be required for ribociclib to be recommended for listing.
- 7.15 The PBAC noted that the [REDACTED] scheme for ribociclib (and the CDK4/6 class of drugs) was proposed to address uncertainties in the economic model and to minimise financial risks to Government. The PBAC considered that the modelling approach used in the re-submission would not be an appropriate basis to inform a future assessment of incremental cost-effectiveness. In terms of the [REDACTED], the PBAC regarded the [REDACTED]. However, noting that the mature OS results are not expected to be available before 2020, the PBAC stated that the proposed scheme would not provide a conclusion in a reasonable timeframe, so that, overall it was preferable for the estimate of cost effectiveness to be based on a less optimistic extrapolation of the currently available evidence as outlined above.
- 7.16 The PBAC advised that any future resubmission should address the high and uncertain cost effectiveness by revising the noted parameters of concern in the economic model. Additionally, the PBAC considered that the incremental cost effectiveness of ribociclib would be more acceptable with a base case ICER of \$45,000/QALY - \$75,000/QALY. The associated revised financial forecasts should include a risk share agreement that appropriately limits the financial risk to the Commonwealth.
- 7.17 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

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

## **9 Sponsor's Comment**

Novartis are committed to working with the PBAC to achieve agreement on sustainable PBS listing conditions for ribociclib at the earliest opportunity.