5.12 RIBOCICLIB, 200 mg tablet, Kisqali®, Novartis Pty Ltd.

1 Purpose of Application

1.1 The submission requested an Authority Required listing for ribociclib in combination with letrozole 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).

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

Component	Description
Population	Non pre-menopausal 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	Progression free survival (PFS) Overall survival (OS) Overall response rate (ORR) Health related quality of life Serious adverse events (SAE)
Clinical claim	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, p28 of the submission.

2 Requested listing

2.1 Suggested additions are in italics and suggested deletions are in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	Dispensed price for maximum quantity (DPMQ)	Proprietary Name and Manufacturer	
RIBOCICLIB Tablet 200 mg, 63 Tablet 200 mg, 42 Tablet 200 mg, 21	1	5	 $[redacted] (published) $[redacted] (effective) $[redacted] (published) $[redacted] (effective) $[redacted] (published) $[redacted] (effective)	Kisqali® 	Novartis Pharmaceuticals Australia Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Severity:	~~Advanced or metastatic~~ *Locally advanced inoperable and metastatic*
Condition:	~~Advanced or metastatic~~ breast cancer

PBS Indication:	~~Advanced or metastatic~~ *Locally advanced inoperable and metastatic* breast cancer
Treatment phase:	Initial~~ and continuing~~ *treatment*
Restriction Level / Method:	☒ *Authority Required - In Writing* ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	~~The patient must not have received any prior endocrine therapy for advanced breast cancer~~ *The treatment must be an initial endocrine-based therapy for this indication* *AND* The treatment must be in combination with ~~letrozole~~ *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.*
Population criteria:	~~The~~ 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* *Authority applications for treatment must be made in writing and must include:* *(a) a completed authority prescription form; and* *(b) a completed PBS Supporting Information Form which includes:* *(i) a copy of the pathology reports from an Approved Pathology Authority confirming the presence of hormone receptor and lack of presence of HER2 gene amplification by in situ hybridisation (ISH); and* *(ii) a copy of the signed patient acknowledgement form.*
Administrative Advice	~~Patients with progressive disease with ribociclib are no longer eligible for PBS-subsidised ribociclib.~~ *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.* *Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

Treatment phase:	~~Initial and c~~Continuing *treatment*

Restriction Level / Method:	☐ Authority Required - In Writing ☒ *Authority Required - Telephone* ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	~~The patient must not have received any prior endocrine therapy for advanced breast cancer~~ *Patient must have previously been issued with an authority prescription for this drug for this indication,* *AND* The treatment must be in combination with ~~letrozole~~ *a non-steroidal aromatase inhibitor (NSAI)*
Clinical criteria:	Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug,
Population criteria:	~~The~~ 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*
Administrative Advice	~~Patients with progressive disease with ribociclib are no longer eligible for PBS-subsidised ribociclib.~~ *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.* *Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*

Treatment phase:	~~Initial~~ *Grandfathering treatment*
Restriction Level / Method:	☒ *Authority Required - In Writing* ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	~~The patient must be currently receiving ribociclib via an approved patient access program~~ *Patient must have previously received non-PBS-subsidised treatment with this drug for this indication prior to [listing date];* OR The patient must be receiving their first endocrine-based therapy for ~~advanced breast cancer~~ *this indication*; AND The treatment must be in combination with ~~letrozole~~ *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.
Population criteria:	~~The~~ 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* *Authority applications for treatment must be made in writing and must include:* *(a) a completed authority prescription form; and* *(b) a completed PBS Supporting Information Form which includes:* *(i) a copy of the pathology reports from an Approved Pathology Authority confirming the*

	presence of hormone receptor and lack of presence of HER2 gene amplification by in situ hybridisation (ISH); and *(ii) a copy of the signed patient acknowledgement form.*
Administrative Advice	~~Patients with progressive disease with ribociclib are no longer eligible for PBS-subsidised ribociclib.~~ *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.* *Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au* *Applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*

2.2 The proposed PBS restriction is not in line with the MONALEESA-2 trial population in the following areas:

- Only patients with ECOG performance status 0 or 1 were included in the trial. The PSCR (p.3) agreed to restrict PBS-reimbursed access to patients with an ECOG performance status 0 or 1. A clinical criterion to this effect has been added to the above restriction for initial treatment. The PSCR requested that if a future PBS listing for palbociclib provided subsidised access for patients with ECOG ≥2, that those patients should not be excluded from treatment with ribociclib on the basis of equivalent efficacy of these agents.
- Patients with inflammatory breast cancer or central nervous system metastases were excluded from the trial. The Pre-PBAC response (p.2) proposed that patients with "inflammatory breast cancer or central nervous system metastases" be excluded from PBS-subsidised access to ribociclib.
- Patients were included in the trial 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 PSCR (p.3) acknowledged that patients who are 'truly' endocrine resistant should not be eligible to receive PBAC reimbursed ribociclib in combination with letrozole. However, the PSCR contended that adoption of this specific eligibility criterion would also exclude some patients who were not included in the study for ethical reasons, rather than reasons relating to ability to receive clinical benefit; specifically, patients who relapsed after having responded to standard duration adjuvant endocrine treatment. As such, the PSCR proposed that the PBS restriction for ribociclib include a note to exclude patients who progressed in the first 5 years of adjuvant

therapy and allow patients who have responded to standard of care endocrine therapy in the adjuvant setting (irrespective of whether they have relapsed after responding to their initial 5 years of adjuvant therapy).

2.3 The PSCR (p.3) proposed that the following note be added to the restriction to align with the inclusion criteria of the MONALEESA-2 trial: '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.'

2.4 The evaluation noted there is potential for ambiguity in the term 'advanced breast cancer'. A clearer definition for the proposed population would be more appropriate to avoid leakage into a broader population. The PSCR (p.3) agreed, noting that the vast majority of patients in the MONALEESA-2 study were Stage IV, and that a clearer definition would better isolate Stage III patients of highest clinical need. However, the PSCR also claimed that this change may result in [redacted] As such, the PSCR requested that the PBAC allow these patients to be grandfathered to PBS reimbursed ribociclib at the time of PBS listing. The DUSC noted that the intent of a grandfathered restriction was to only allow access to patients who meet the eligibility criteria for subsidised access. As such, it may not be appropriate to grandfather the Stage III subgroup. The ESC considered that "locally advanced inoperable and metastatic breast cancer" was a better definition of the patient group, and would minimise leakage to patients with less disease severity.

2.5 The submission included a note within the PBS restriction that patients whose disease progressed on ribociclib would no longer be eligible for PBS-subsidised ribociclib. The PSCR agreed to the addition of a continuing telephone authority restriction as a replacement for the proposed note. The Pre-PBAC response proposed that for further alignment with the inclusion criteria of the MONALEESA-2 trial, the RECIST 1.1 assessment criteria be used to evaluate response to treatment.

2.6 The PSCR (p.3) noted that the sponsor accepted the other Secretariat suggested changes to the restriction, including allowing ribociclib to be used in combination with any non-steroidal aromatase inhibitor (NSAI, i.e. letrozole or anastrozole). The DUSC agreed that allowing ribociclib to be used in combination with any NSAI was appropriate as ribociclib would be used in the same patient population as palbociclib.

2.7 The submission also proposed a grandfathering restriction for patients who are currently receiving a first-line of endocrine based therapy for advanced or metastatic breast cancer via the PBS. The proposed TGA indication specifies that patients should be treated with ribociclib plus letrozole as 'initial endocrine-based therapy'. The DUSC agreed with the evaluation that under the proposed TGA indication, grandfathering existing patients on first-line endocrine therapy to ribociclib may not be appropriate. The pre-PBAC response (p.1-2) proposed that in the interest of

aligning the restriction criteria more closely with the MONALEESA-2 trial and [redacted], the PBS restriction for ribociclib should exclude patients with >28 days of treatment with an NSAI for their ABC prior to initiation of ribociclib.

2.8 The requested basis for listing was a cost-utility analysis for ribociclib + letrozole compared with letrozole alone. The submission also presented a cost-minimisation analysis compared with a near market comparator, palbociclib plus letrozole.

2.9 Ribociclib is administered orally as tablets. The recommended dosing regimen is 600 mg once daily (three tablets of 200 mg) for 21 days, followed by 7 days off treatment to complete a 28-day cycle. In the event of adverse drug reactions, the starting dose of ribociclib may be reduced to 400 mg once daily (two tablets of 200 mg), and further to 200 mg once daily (one tablet of 200 mg) if required. The ESC noted that the majority of patients in the MONALEESA-2 trial ([redacted] June 2016 dataset) had a dose interruption or change. Letrozole (2.5 mg once daily) is to be taken alongside ribociclib for the full 28-day cycle. Patients are treated until disease progression.

2.10 The submission included a request for special pricing arrangement (SPA) for ribociclib. The submission proposed effective prices which are [redacted]% lower than the published prices.

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

3 Background

3.1 TGA status at time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process. At the time of the evaluation, no TGA documents were available. The Round 2 TGA Clinical Evaluator's Report was received on 2 June 2017. The proposed TGA indication is "Treatment of postmenopausal women with HR+, HER2- ABC in combination with letrozole as initial endocrine-based therapy." The TGA Delegate's overview was not received in time for PBAC consideration.

3.2 The PBAC has not previously considered ribociclib.

3.3 Palbociclib, a near market comparator in the same therapeutic class as ribociclib, was listed on the ARTG on 3 May 2017 for the treatment of HR+, HER2- ABC in combination with:

- an aromatase inhibitor as initial endocrine-based therapy
- fulvestrant in patients who have received prior therapy.

3.4 Palbociclib, in combination with an NSAI (letrozole or anastrozole), was not recommended by the PBAC at its March 2017 meeting as an initial endocrine-based therapy in post-menopausal HR+, HER2-, ABC patients on the basis that on the basis of the following:

- The PBAC did not know the circumstances that palbociclib would be registered for use in Australia.

- There is strong clinical benefit of endocrine-based therapy alone as first-line therapy in many patients, and uncertainty as to which patients would most benefit from the addition of palbociclib.
- A number of effective and well-tolerated second-line therapies (including oral treatments) are available for patients who progress after first-line endocrine-based therapy.
- Palbociclib is associated with significant toxicity.
- The effect of palbociclib on overall survival (OS) is uncertain.
- Palbociclib is associated with high and uncertain cost-effectiveness.
- The likely net cost of listing palbociclib to the PBS would be $50-$75 million in the first year and more than $100 million per year in the subsequent four years, and as such, there would be a significant opportunity cost to the Commonwealth.

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+/HER2- molecular subtype, which is associated with favourable prognosis due to its responsiveness to hormonal/endocrine therapy. However, the submission claimed that development of endocrine resistance is limiting the efficacy of current therapies, which eventually leads to disease progression. The ESC considered that a number of effective and well-tolerated second-line therapies (including oral treatments) are currently available on the PBS for patients who progress after first-line endocrine-based therapy.

4.2 The submission proposed the addition of ribociclib, a CDK 4/6 inhibitor, in combination with letrozole, for the treatment of non-premenopausal, HR+ and HER2-, ABC patients currently treated with an NSAI as first-line endocrine-based therapy. While palbociclib was proposed for listing in combination with any NSAI, the clinical evidence presented in this submission and the requested PBS restriction are specific to a particular NSAI (letrozole). The sponsor of ribociclib is also the sponsor of a brand of letrozole listed on the PBS (Femara®) but is not the sponsor of any of the PBS-listed brands of anastrozole. The PSCR (p.3) agreed that the proposed restriction should be broadened to include all NSAIs. The ESC 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 therapeutic relativity sheets state that anastrozole, for the treatment of ABC in post-menopausal women, was recommended on a cost minimisation basis compared with letrozole.

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

5 Comparator

5.1 The submission proposed letrozole alone to be the main comparator for ribociclib + letrozole on the basis that letrozole is the most commonly prescribed first line therapy for HR+, HER2- ABC. The ESC considered this was appropriate.

5.2 The submission also nominated palbociclib plus letrozole as a near market comparator as it is of the same therapeutic class with similar indication. The ESC considered that palbociclib was an appropriate near market comparator.

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

6 Consideration of evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. At the hearing, a clinician discussed the natural history of the disease, reflected on patient experience to emphasize ribociclib's efficacy in slowing disease progression, and addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on ribociclib's place in therapy.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals described a range of benefits of treatment with ribociclib including improved quality of life, manageable side effects, slower disease progression leading to delay in chemotherapy, but also noted its very high financial cost.

6.3 The Breast Cancer Network Australia (BCNA) indicated that the benefits of ribociclib treatment included the convenience of oral therapy (particularly in rural areas), a claim of lower toxicity profile compared with chemotherapy, and slower disease progression. The Medical Oncology Group of Australia (MOGA) also expressed its support for the ribociclib submission, on the basis of the PFS benefit, and considered that the patient population targeted in the MONALEESA-2 trial was appropriate. The correspondence from MOGA stated that the treatment regimen and toxicity profiles of ribociclib and palbociclib were very similar, however abemaciclib, a third CDK 4/6 inhibitor, which is dosed continuously, may have a lower risk of treatment-associated neutropenia. Both BCNA and MOGA claimed that ribociclib treatment-related neutropenia did not carry the same clinical or economic cost implications as chemotherapy-related neutropenia, and was manageable by dose reduction.

6.4 The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for ribociclib in combination with letrozole, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with letrozole alone. 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.

6.5 Representatives of the PBAC also met with BCNA prior to the PBAC meeting. The meeting covered the upcoming PBAC consideration of ribociclib. The following points provide a summary of the perspectives presented by the Breast Cancer Network Australia (BCNA) to PBAC representatives:

- The condition affects the quality of life for patients and their families, impacting on their social, economic and psychological wellbeing, with few new medicines becoming available in recent years;
- Patients with this condition and their treating doctors claimed that CDK inhibitors are available for breast cancer in many other countries. The BCNA was aware that ribociclib is under review by the TGA, but welcomed the TGA registration of palbociclib in Australia;
- Whilst acknowledging that the clinical trials for CDK inhibitors like palbociclib and ribociclib are ongoing, and are yet to demonstrate an improvement in quality of life or an overall survival benefit, patients value the demonstrated progression-free survival outcomes, and view these medicines as well-tolerated treatment options that delay disease recurrence and the eventual onset of cytotoxic chemotherapy;
- Notwithstanding the PBAC's concerns regarding the significant toxicities associated with palbociclib treatment, patients indicated that the most common adverse events experienced with CDK inhibitors (fatigue and febrile neutropenia) are substantially less detrimental than those experienced while receiving chemotherapy (mouth ulcers, fatigue and infection). Furthermore, the adverse effects of cytotoxic chemotherapy have prevented many women suffering from this condition from remaining in the workforce or living their life with their families;
- Without PBS subsidised access, the high cost of palbociclib and ribociclib would prohibit most patients from accessing these medicines. Although sponsor-supported compassionate access programs exist, these are difficult to access, and are particularly inequitable for patients from rural areas; and
- The BCNA indicated that they were willing to work together with the sponsors, consumers, PBAC and MOGA to initiate dialogue via stakeholder meetings, in order to facilitate PBS-subsidised access to CDK inhibitors for this condition.

[1] Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 26:1547-73, 2015

Clinical trials

6.6 The 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).

6.7 In addition, two randomised trials were provided as part of an indirect secondary comparison of ribociclib and palbociclib, using letrozole alone as a common comparator.

- PALOMA-1: a phase II, randomised, open-label trial of palbociclib + letrozole for first line treatment of 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.

6.8 Details of the trials presented in the submission are provided in the following table.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial vs. placebo		
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. • Executive Summary for interim 90 Day Update: Data cut off 18 Aug 2016, report date 13 Sep 2016. • Second Overall Survival Interim Analysis: Data cut off 2 Jan 2017, report date 11 Feb 2017. Publication: Hortobagyi, Stemmer et al. 2016. Ribociclib as First line Therapy for HR-Positive, Advanced Breast Cancer.	 27 July 2016 13 Sept 2016 11 Feb 2017 NEJM 2016; 375 (17): 38-48
Supplementary randomised trials for indirect comparison palbociclib plus letrozole vs. letrozole alone		
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. 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. Bell, T Crown, JP Lang, I Bhattacharyya, H Zanotti, G Randolph, S Kim, S Huang, X Bartlett, CH Finn, R Slamon, D. Impact of adding palbociclib to letrozole on pain severity and pain interference with various activities of daily life in patients with ER+, HER2- metastatic breast cancer as first line treatment. 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	Lancet Oncol 2015; 16:25-35. Breast Cancer Research (2016) 18:67. Cancer research (2015) 75:9 SUPPL.1 Current Medical Research and Opinion 2016; 32:5, 959-965.
PALOMA-2 A5481008 [NCT01740427]	Finn, Martin et al. 2016. Palbociclib and Letrozole in Advanced Breast Cancer. 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	NEJM 2016; 375: 1925-1936. J Clin Oncol 34, 2016 (suppl; abstract 507). An Oncol 27 (suppl_6): 225PD

Source: Table2.3 p 53 of the submission.

6.9 The key features of the direct and indirect randomised trials are summarised in the following table.

Table 3: 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
DIRECT EVIDENCE: Ribociclib + letrozole vs. letrozole						
MONALEESA-2	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	Investigator assessed PFS and OS used in model. PFS, ORR and AEs used in indirect comparison.
Jun 2016 interim analysis		20.1 months			Primary: investigator assessed PFS Secondary: ORR, CBR, AEs	ORR used in model. PFS, ORR and AEs used in indirect comparison.
Jan 2017 interim analysis		26.4 months			Primary: investigator assessed PFS Secondary: OS	Used for validation purposes only.
INDIRECT EVIDENCE: Palbociclib + letrozole vs. letrozole						
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	Used in indirect comparison for cost-minimisation
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 Three interim analyses were conducted for the MONALEESA-2 trial. While the primary outcome measure was the same for all three analyses (investigator assessed PFS), different secondary outcomes were assessed at each analysis (see Table 3 above). The PFS and OS results from the first interim analysis (January 2016), and the overall response rate (ORR) results from the second interim analysis (June 2016), were used in the economic model. The PFS, ORR and AE results from the second interim analysis were used in the indirect comparison. The next MONALEESA-2 interim analysis of OS is planned after approximately 300 deaths have been observed, with a final analysis conducted after approximately 400 deaths have been observed. Based on expected event rates, the final OS analysis is unlikely to be available until 2020.

6.11 PALOMA-1 outcomes (objective response, PFS and PROs) are potentially subject to bias due to the trial being open label. The evaluation considered that the PALOMA-2 outcomes were more robust for the indirect comparison with MONALEESA-2.

Comparative effectiveness

6.12 The table below presents PFS results for the direct comparison of ribociclib + letrozole to letrozole alone using the MONALEESA-2 trial data at all available time points.

Table 4: Results of PFS (Investigator and BICR) 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) [a]
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
Investigator Jan 2017	140/334 (41.9)	205/334 (61.4)	25.3 (23.0, 30.3)	16.0 (13.4, 18.2)	9.3	0.568 (0.457, 0.704) p-value <0.0001

BICR: Blinded Independent Central Review; CI: Confidence Interval; HR = Hazard Ratio; NR=not reported.
[a] hazard ratio < 1 indicates a reduction in hazard rate in favour of ribociclib + letrozole
Source: Section 2.5.1.1.1, p70-73 of the submission and calculated during the evaluation.

6.13 The table below presents OS results from the MONALEESA-2 trial at all available time points. Survival data were immature; in the most recent January 2017 interim analysis only 15.0% and 19.8% of patients treated with ribociclib + letrozole and letrozole alone had died, respectively. The difference in OS between ribociclib + letrozole and letrozole alone was not statistically significant. The PSCR (p.1) argued that the results of the second OS interim analysis numerically favour the ribociclib + letrozole arm, with a 25.4% risk reduction relative to placebo (HR 0.746; 95% CI: 0.517, 1.078). The PSCR further contended that although OS data are not mature, the available data show consistent PFS HRs between interim analyses and a strong trend towards improved OS after 106 events. The ESC agreed that these data demonstrated a trend for improved OS in favour of ribociclib + letrozole, but considered that the OS 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.

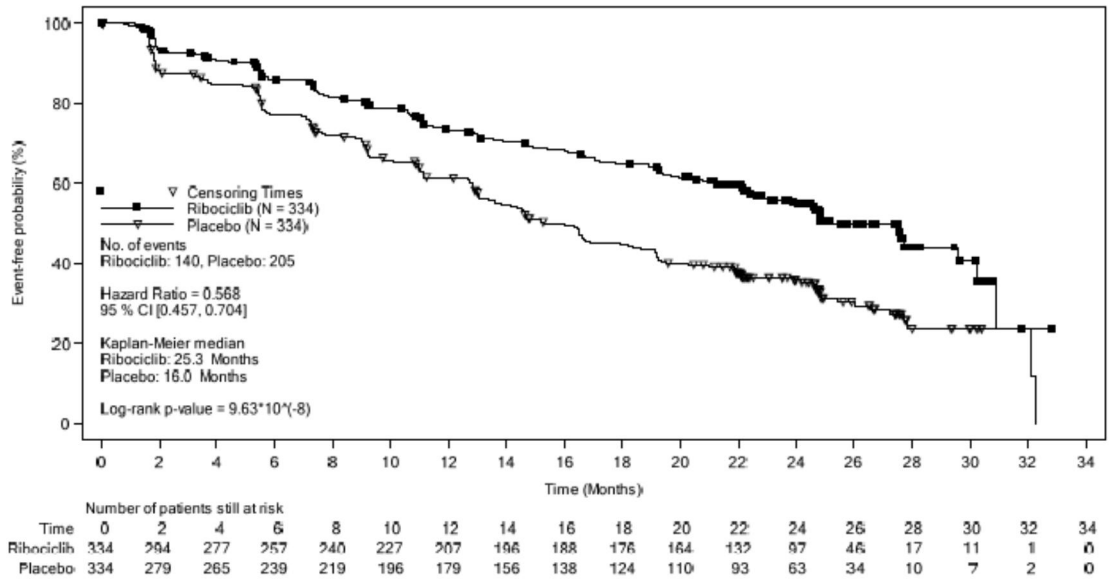
Table 5: Results of OS from MONALEESA-2

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) [a]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Jan 2017	50/334 (15.0)	66/334 (19.8)	NR	NR	NR	0.746 (0.517, 1.078) p-value 0.059

CI: confidence interval; NR: not reported, HR: Hazard Ratio; OS: overall survival.
[a] hazard ratio < 1 indicates a reduction in hazard rate in favour of ribociclib + letrozole.
Source: Table 2.19 and Table 2.20, Section 2.5.of the submission.

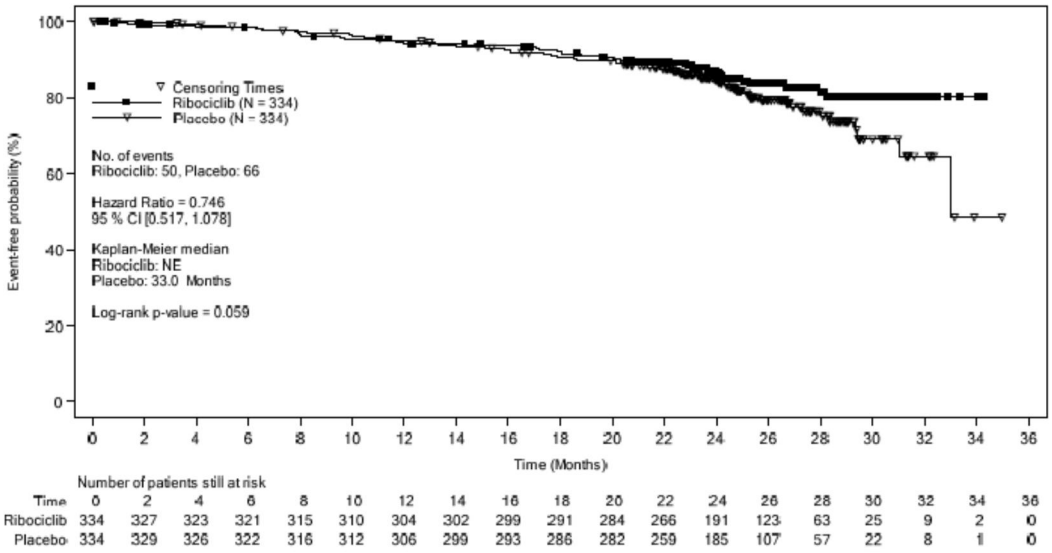
6.14 The Kaplan-Meier plots for investigator assessed PFS and OS from the most recent analysis for the MONALEESA-2 trial are presented below.

Figure 1: MONALEESA-2 Kaplan Meier Plot of PFS (investigator assessed, Jan 2017 interim analysis)



Source: Figure 2.9, p 73 of the submission.

Figure 2: MONALEESA-2 Kaplan Meier plot of OS (Jan 2017 interim analysis)



Source: Figure 2.11 p76 of the submission.

6.15 The ESC noted that MONALEESA-2 measured quality of life using the EORTC QLQ30 and the EQ-5D-5L. The results for the EORTC QLQ30 revealed no significant effect of treatment, time or treatment by time interactions. The estimated mean difference in changes to global health status/QoL scale score between the two treatment arms was -1.50 (95% CI: -4.0, 1.0). No EQ-5D-5L results were provided in the submission that demonstrated a change from baseline and difference between treatment groups.

6.16 Details of the indirect comparison presented in the submission are provided in the table below. The submission presented six different indirect comparison estimates using PALOMA-1 alone, PALOMA-2 alone, meta-analysis of PALOMA-1 and PALOMA-2, and the MONALEESA-2 January and June 2016 interim results.

Table 6: Summary of results of the indirect comparison (PFS, ribociclib + letrozole vs. palbociclib + letrozole)

Trial type or estimate	Trial ID	*n* with event/*N* (%)	Letrozole *n* with event/*N* (%)	HR (95%CI)
Ribociclib + letrozole vs. letrozole alone trials	MONALEESA-2 -Investigator assessed PFS, Jan 2016	93/334 (27.8)	150/334 (44.9)	HR 0.556 (0.429, 0.720) p-value <0.0001
	-Investigator assessed PFS, June 2016	118/334 (35.3)	179/334 (53.9)	HR 0.559 (0.443, 0.706) p-value <0.0001
Palbociclib + letrozole vs. letrozole alone trials	PALOMA-1 Investigator assessed PFS	41/84 (48.8)	59/81 (72.8)	0.488[a] (0.319, 0.748) p-value 0.0004
	PALOMA-2 Investigator assessed PFS	194/444 (43.7)	137/222 (61.7)	0.58[a] (0.46, 0.72) p-value <0.001
	Pooled (Meta analysis)	[redacted]	[redacted]	[redacted]
Indirect estimate of effect adjusted for the common reference				**HR[b] (95%CI)**
Monaleesa-2 (JAN) vs. PALOMA-1				[redacted]
Monaleesa-2 (JAN) vs. PALOMA -2				[redacted]
Monaleesa-2 (JAN) vs. PALOMA -1 & 2				[redacted]
Monaleesa-2 (JUN) vs. PALOMA -1				[redacted]
Monaleesa-2 (JUN) vs. PALOMA -2				[redacted]
Monaleesa-2 (JUN) vs. PALOMA -1 & 2				[redacted]

CI: confidence interval; n: number of participants with event; N: total number of participants in group; HR: hazard ratio
[a] 1-sided p-value
[b] hazard ratio < 1 indicates a reduction in hazard rate in favour of ribociclib + letrozole.
Source: Finn 2016 p1930-32, Finn 2015 p31, Section 2.5.1.1.1, p70-73 of the submission and Table 2.38, p96 of the submission

6.17 Based on the indirect comparison there was no significant difference between ribociclib and palbociclib for PFS. However, the ESC considered that a lack of evidence of a significant difference is not equivalent to evidence of no difference (non-inferiority). No minimally clinically important difference was proposed, the outcomes were not formally tested for non-inferiority and no non-inferiority margin was nominated.

6.18 The ESC considered that the results of the indirect comparison should be considered with caution as the PALOMA-1 trial was open label and subject to bias. Furthermore, there were differences in the population characteristics across MONALEESA-1 and PALOMA-1 and PALOMA-2, and OS and AEs in the common comparator arm (letrozole alone). These differences suggest that the trials have limited exchangeability.

Comparative harms

6.19 Significantly more patients treated with ribociclib + letrozole compared with letrozole alone had serious AEs, Grade≥3 AE, Grade≥3 AE 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. The incidence of AEs in the MONALEESA-2 trial are summarised in the table below.

Table 7: 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 (%)	Relative risk (95% CI)
All AEs	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]
Grade≥3 AE	[redacted]	[redacted]	[redacted]
Grade≥3 AE requiring treatment	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]
AEs requiring dose change/interruption	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]
On treatment deaths*	[redacted]	[redacted]	[redacted]

AE: Adverse event; n: patients with event; N: total patients.
*Note: based on small patient numbers
Source: Table 2.26, Section 2 of the submission and calculated during the evaluation

6.20 In the MONALEESA-2 trial, the most commonly reported AEs were neutropenia ([redacted]%), nausea ([redacted]%) and fatigue ([redacted]%). There were also some reports of serious AEs, such as febrile neutropenia (1.5%) and on-treatment deaths (see below). The ESC considered that the high incidence of neutropenia may be manageable in clinical practice as it is rapidly reversible and dose dependent. The ESC further noted the relatively rare instances of febrile neutropenia.

6.21 The submission also reported indirect comparisons between ribociclib and palbociclib for AEs (Grade≥3 and discontinuation due to AE). Ribociclib + letrozole was associated with a similar number of Grade≥3 AEs, but a greater number of AEs leading to treatment discontinuation compared with palbociclib + letrozole.

6.22 The submission provided additional data on potential safety concerns beyond those identified in the clinical trials. As part of the TGA application, additional data on a further 187 patients who received treatment with ribociclib at the 600 mg daily dose in a series of monotherapy studies (across various patient populations) were also pooled in order to provide better information about the safety profile of ribociclib. Of the 568 patients in the safety population [redacted] died while on treatment. Treatment discontinuation as a result of AEs was more evident for ribociclib + letrozole [redacted] compared with letrozole alone [redacted].

6.23 The TGA application lists the following as AEs of special interest that should be monitored carefully with dose reductions as appropriate: hepatobiliary toxicity (24.0% ribociclib + letrozole versus 13.6% letrozole alone), inducement of QT interval prolongation (7.5% ribociclib + letrozole versus 2.4% letrozole alone), neutropenia including Grade≥3, (56.9% ribociclib + letrozole versus 0.9% letrozole alone) and febrile neutropenia. A complete blood cell count is required for patients prior to commencing treatment with ribociclib to manage this risk and it should be repeated every 2 weeks for the first two treatment cycles, at the beginning of each subsequent 4 week cycle, and then as clinically indicated.

Benefits and harms

6.24 A summary of the comparative benefits and harms for ribociclib + letrozole versus letrozole alone is presented in the table below.

Table 8: Summary of comparative benefits and harms for ribociclib + letrozole and letrozole alone

Benefits					
Event	**Ribociclib + letrozole**	**Letrozole**	**Absolute Difference**	**HR (95% CI)**	
PFS - BICR Jan 2016 (MONALEESA-2)					
Progressed	NR	NR	-	0.592 (0.412, 0.852)	
Median, months	NR	NR	NR		
PFS - investigators assessed Jan 2017 (MONALEESA-2)					
Progressed	140/334 (41.9)	205/334 (61.4)	-	0.568 (0.457, 0.704)	
Median (95% CI), months	25.3 (23.0, 30.3)	16.0 (13.4,18.2)	9.3		
OS Jan 2017 (MONALEESA-2)					
Died	50/334 (15.0)	66/334 (19.8)	-	0.746 (0.517, 1.078)	
Median, months	NR	NR	NR		
Harms					
	Ribociclib + letrozole	**Letrozole**	**RR (95% CI)**	**Events/100 patients**	
				Ribociclib + letrozole	**Letrozole**	**RD (95% CI)**
Grade≥3 AE						
MONALEESA-2 Jun 2016	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia						
MONALEESA-2 Jun 2016	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade≥3 neutropenia						
MONALEESA-2 Jun 2016	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea						
MONALEESA-2 Jun 2016	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue						
MONALEESA-2 Jun 2016	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia						
MONALEESA-2 Jan 2016	5/334	0/330	-	1.5	0.0	1 (0, 3)

HR: Hazard Rate Ratio; OS: Overall Survival; PFS: Progression-free Survival; RD: risk difference; RR: relative risk; Source: Compiled during the evaluation and p71, Table 2.18 p73, Table 2.20 p76 and calculated during the evaluation and Table 12-17 of Interim_CSR_Jan 2016.pdf.

6.25 On the basis of direct evidence presented by the submission, at a median follow-up of around 20 months, there would be approximately nine months improvement in median PFS) in patients treated with ribociclib + letrozole in comparison with letrozole alone. A trend to improvement in OS was observed, but was based on immature data and was not statistically significant.

6.26 For every 100 patients treated with ribociclib + letrozole in comparison with letrozole alone, over a median follow-up of around 20 months, approximately:

- 49 additional patients would experience a Grade≥3 adverse event;
- 59 additional patients would experience any grade of neutropenia;
- 49 additional patients would experience Grade≥3 neutropenia;

- 24 additional patients would experience nausea;
- 7 additional patients would experience fatigue; and
- 1.5 additional patients would experience febrile neutropenia.

Clinical claim

6.27 The submission claimed that ribociclib + letrozole provides superior efficacy and inferior safety compared with letrozole alone based on direct evidence.

6.28 The clinical claim regarding efficacy is premature because median OS has not yet been reached, with final analysis not expected until approximately 2020. In the most recent January 2017 interim analysis, only 15.0% and 19.8% of patients treated with ribociclib + letrozole and letrozole alone had died, respectively. Interim results indicate OS favours ribociclib + letrozole compared with letrozole alone but the difference is not statistically significant. The ESC noted that the investigator assessed PFS was significantly improved in the ribociclib + letrozole arm compared with letrozole alone (HR of 0.568, 95% CI: 0.457, 0.704) and that the median PFS was 25.3 versus 16.0 months in the ribociclib + letrozole arm vs. letrozole alone arms, respectively.

6.29 The ESC considered the claim of inferior safety was reasonable, with the majority of ribociclib + letrozole patients in the MONALEESA-2 trial experiencing Grade≥3 AEs AEs ([redacted]%, compared with [redacted]% for letrozole alone). The PSCR (p.1) argued that the AEs were mostly asymptomatic, predictable and manageable. The ESC agreed that the high incidence of neutropenia may be manageable in clinical practice as it is rapidly reversible and dose dependent and noted that dose interruptions and reductions would be part of the standard management of patients on a CDK4/6 inhibitor + NSAI combination. The PSCR noted that quality of life was not adversely affected as a result of AEs in the MONALEESA-2 trial. Conversely, the ESC noted that quality of life was not improved as a result of treatment with ribociclib + letrozole, compared with letrozole alone.

6.30 The submission also claimed that ribociclib + letrozole was non-inferior in efficacy and safety compared with palbociclib + letrozole based on indirect evidence. This indirect clinical claim regarding efficacy is also premature. Based on the indirect comparison there was no significant difference between ribociclib and palbociclib for PFS. However, a lack of evidence of a significant difference is not equivalent to evidence of no difference (non-inferiority), and a non-inferiority margin was not nominated by the submission. Two of the trials are immature (MONALEESA-2 and PALOMA-2) and had not reached median OS. There was no significant difference identified in patients experiencing Grade≥3 AEs, however there were more treatment discontinuations resulting from AEs for ribociclib + letrozole, which was statistically significant; the claim of non-inferior safety was therefore not supported. The indirect comparison is also subject to exchangeability limitations resulting from baseline differences between the trials on characteristics shown to be related to PFS, and event rates in the common reference group that differed between trials. The

ESC agreed with the evaluation and advised that the submission's claim of non-inferiority over palbociclib was not adequately supported.

6.31 The PBAC advised that while the submission's claim of superior efficacy compared with letrozole alone was reasonable for PFS, the immaturity of the OS data resulted in a high degree of uncertainty in the assessment of the magnitude of long-term benefit.

6.32 The PBAC noted the limited exchangeability of the trials included in the indirect comparison with palbociclib presented in the submission. The PBAC further 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 the submission's claim of non-inferiority against palbociclib was not adequately supported.

Economic analysis

6.33 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.

6.34 The ESC noted that the PSCR provided an updated economic model based on the January 2017 data, which reported an ICER of $75,000/QALY – $105,000/QALY gained. The ESC 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 ($105,000/QALY – $200,000/QALY gained) as the extrapolation approach differed between the two economic models.

6.35 Additionally, the ESC noted that the ICER provided in the PSCR was sensitive to the choice of functional form for the extrapolation, and that the use of a Weibull function in the ICER provided in the PSCR resulted in a lower ICER than other functions. The ESC considered that the updated model required evaluation via a subsequent major submission. The remainder of this section relates to the economic model presented in the submission. The pre-PBAC response (p.1) stated that a major resubmission would be submitted for the PBAC's consideration at its November 2017 meeting to allow full evaluation of the updated model.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case vs. 15.3 months (median) in the MONALEESA-2 trial, which is ongoing. This was not reasonable, given the disproportionately short follow-up time in the trial, and the non-significant difference in the OS between the two treatment arms. In previous submissions for ABC where there was a non-significant difference in OS, although for later line treatment, the time horizon was 3 years (everolimus, 2013 and paclitaxel, 2008).
Outcomes	PFS, OS, QALYs and LYs
Methods used to generate results	Partitioned survival model
Health states	• Pre-progression: - In both treatment groups, this is further partitioned by response status (OR vs. SD) - Within the RIB+LTZ group only, this is further partitioned by continued ribociclib treatment status (on

Component	Summary
	vs off) • Post-progression • Dead
Utilities	Based on EQ-5D-5L data obtained from the MONALEESA-2 trial
Cycle length	1 month (30.44 days)
Survival rates	Overall response was based on the MONALEESA-2 trial (June 2016, investigator assessed) and did not vary over time. The evaluation noted that it would be preferable if the model was updated to the January 2017 interim analysis, which was included in the PSCR. The details below relate to the economic model in the submission, rather than in the PSCR. PFS and OS rates were used to quantify the proportions of patients in the Pre-progression and Death health states, respectively. The current approach in the model underestimates the proportion of patients in the Post-progression health state due to truncation of the probability of death. A more appropriate approach is to estimate post-progression survival using patient-level data from the MONALEESA-2 trial. PFS: Used PFS data (January 2016, investigator assessed) from the MONALEESA-2 trial for the first 14 months. Extrapolated based on a parametric function (lognormal) fitted to the data from the MONALEESA-2 trial. The evaluation noted that it would be preferable if the model was updated to the January 2017 interim analysis. OS, letrozole alone: Used OS data from Dickler et al. (2016) for the first 35 months, then extrapolated to ten years (the evaluation incorrectly stated that this was based on MONALEESA-2 for the first 35 months and then extrapolated using data from Dickler (2016)). The evaluation noted that it would be preferable if the model was updated to the January 2017 interim analysis. Extrapolated based on a parametric function (lognomal) fitted to the data from Dickler et al (2016). The use of external data introduces uncertainty. The OS rates using Dickler data are lower than the OS rates using the MONALEESA-2 trial. OS, ribociclib + letrozole: Applied a HR from the power calculation for the MONALEESA-2 trial (0.72). The ESC considered the choice of the hazard ratio of 0.72 was not adequately justified, and the approach assumes proportional hazards, which was also not justified. Treatment continuation was based on the MONALEESA-2 trial (date not reported) for the first 14 months. It was then extrapolated based on a parametric function (exponential) fitted to the data from the MONALEESA-2 trial. The exponential function had the worst goodness-of-fit compared with other parametric functions tested.
Costs	The model included: Drug acquisition costs for the respective treatment regimens; the cost of monitoring patients and managing clinically relevant related AEs; comparative costs of other post-progression anti-cancer therapy (PPACT); other costs associated with the management of ABC; and end of life costs. The submission assumed that the PPACT, other direct healthcare costs associated with disease management (e.g. specialist visits), and end of life costs were equal between groups and zero in the base case based on the limited information regarding differences between interventions. This was not appropriate. Total treatment costs have been underestimated as PFS and OS are longer in the ribociclib + letrozole group, which has underestimated the ICER in favour of ribociclib. No G-CSF costs are included to treat/prevent neutropenia and febrile neutropenia, which favoured ribociclib.

HR: Hazard rate ratio; LTZ: letrozole; LY: life years; PFS: progression free survival; QALY: quality-adjusted life years; OR: overall response; OS: overall survival; RIB: ribociclib; SD: stable disease. Source: compiled during the evaluation.

6.36 Figure 3 shows the extrapolation of PFS in the letrozole alone and ribociclib + letrozole groups based on the lognormal function fitted to data obtained from the MONALEESA-2 trial. Figure 4 shows the extrapolation of OS in the letrozole alone group based on the lognormal function fitted to study data using Dickler et al (2016). It also shows the estimation of OS in the ribociclib + letrozole group based on the OS

in the letrozole alone group and applying a hazard ratio of 0.72 based on the power calculation in the MONALEESA-2 trial. These extrapolations were used in the base case analysis.

Figure 3: Extrapolation of PFS in the letrozole alone and ribociclib + letrozole groups based on the lognormal function fitted to data from the MONALEESA-2 trial

Source: Graph generated by the Evaluator using data in the Excel workbook (sheets PFS_Obs and PFS_Mod).

Figure 4: Extrapolation of OS in the letrozole alone group based on the lognormal fitted to data obtained from the study by Dickler et al (2016) and estimation of OS group based on the OS in the letrozole alone group and a hazard ratio estimated based on the MON

Source: Graph generated by the Evaluator using data in the Excel workbook (sheet OS_Obs, OS_Mod and OS_Est).

6.37 Key drivers of the model are provided in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Time horizon	10 years; extrapolated from 15 months	High, favours ribociclib
Estimation of OS in patients receiving ribociclib + letrozole	In the base case a hazard ratio was applied from the power calculation in the MONALEESA-2 trial (HR=0.72), in comparison to using the OS data and fitting a parametric function.	High, favours ribociclib
Extrapolation of OS in patients receiving letrozole alone	Extrapolation of Dickler (2006) using the lognormal function, in comparison to fitting a parametric function to MONALEESA-2.	High, favours ribociclib
Extrapolation of treatment continuation survival in patients receiving ribociclib + letrozole	Based on the exponential function.	High, favours ribociclib

Source: compiled during the evaluation

6.38 The ESC considered that a time horizon shorter than 10 years would be appropriate given the immaturity of the existing OS data and that any increase in OS was uncertain at the moment. The ESC noted that the ICER was sensitive to the time horizon (see Table 12). While the data presented in the PSCR reduced some of this uncertainty, the ESC felt the OS data were still immature and subject to considerable uncertainty. The pre-PBAC response (p.3) argued that the time horizon of 10 years already accounted for the uncertainty in the extrapolated period, by reducing the clinically plausible period of benefit from 20 years to a more conservative 10 years.

6.39 Results of the economic evaluation are provided in the table below. No stepped analysis was presented in the submission.

Table 11: Results of the economic evaluation

Outcome	Ribociclib +letrozole	Letrozole	Incremental
Costs	$ [redacted]	$ [redacted]	$ [redacted]
LYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost per LY gained			$ [redacted]
Incremental cost per QALY gained			**$** [redacted]

LY: Life years; QALYs: quality adjusted life years. Source: Table 3.32 (p. 144) of the submission

The redacted table shows ICERs in the range of $105,000 - $200,000/QALY.

6.40 The results of key sensitivity analyses are provided in the table below.

Table 12: Results of key sensitivity analyses

Analysis	Worst case		Best case	
	Value	$ per QALY gained	Value	$ per QALY gained
Time horizon (base case = 10 years)	5 years	$	20 years	$
Parametric function used to extrapolate OS in the letrozole group (base case = lognormal)	Exponential	$	Weibull	$
Parametric function used to extrapolate treatment continuation survival (base case = exponential)	Lognormal	$	Weibull	$
Data source used to estimate the HR of OS in the ribociclib + letrozole group compared with the letrozole group alone (base case = power calculation of MONALEESA-2 = 0.72)	PALOMA-1 (0.813)	$	2nd interim analysis of MONALEESA-2 (0.746)	$
Data used to estimate OS in the letrozole group (base case = Dickler 2006)	MONALEESA-2 trial	$	-	-
OS direct extrapolation point (base case = 35 months)	20 months	$	10 months	$
Utility weights data source (base case = MONALEESA-2)	Reed	$	Lloyd	$
RDI of ribociclib (base case = %)	%	$	%	$

HR: Hazard rate ratio; OS: overall survival; RDI: relative dose intensity. Source: Table 3.34 (p. 146) of the submission

6.41 During the evaluation, a multivariate sensitivity analysis was conducted to examine the impact of using data from the MONALEESA-2 trial to extrapolate the OS in both treatment arms, from 36 months to a time horizon of 10 years; the resulting ICER was more than $200,000/QALY gained. Overall the ICER was most sensitive to the time horizon, and the approach used to estimate PFS and OS.

6.42 The submission also presented a cost-minimisation analysis comparing ribociclib + letrozole and palbociclib + letrozole. The estimation of equi-effective doses were based on mean RDI and regimen intensity per cycle. The submission calculated the equi-effective doses to be ribociclib 364.05 mg and palbociclib 87.38 mg .

6.43 The 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. The PSCR (p.7) disagreed, arguing that the RDIs applied in the analysis reflected the average dose of the respective medicines received in the relevant randomised controlled trials, accounting for dose reductions, interruptions and drug holidays.

6.44 No additional costs or offsets were included in the cost-minimisation analysis. The submission claimed that, based on available prescribing information and clinical trials, it is anticipated that ribociclib and palbociclib will have similar administration, monitoring and safety management requirements in clinical practice. The evaluation considered this was not reasonable, given that ribociclib may have inferior safety compared with palbociclib.

Drug cost/patient/course: $[redacted]

6.45 Assuming a cost of $[redacted] per pack of [redacted] tablets, one pack is used per [redacted] days, no dose reduction, and the patient is treated for 25.3 months (median PFS from January 2017 interim analysis of MONALEESA-2) until disease progression. Accordingly, approximately [redacted] packs (adjusted to a full pack) are required for a course of treatment, costing $[redacted] (or $[redacted] per year, assuming [redacted] packs per year of treatment).

Estimated PBS usage & financial implications

6.46 This submission was considered by DUSC. The submission used an epidemiological 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 an [redacted]% relative dose intensity based on the MONALEESA-2 trial.

Table 13: Estimated use and financial implications of listing ribociclib on the PBS schedule

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 2023
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of ribociclib alone						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for substituted/additional endocrine therapy						
Cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less co-payments	$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Estimated financial implications to MBS for monitoring of ribociclib use						
Cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Overall net financial implications to the Australian Government health budget						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to Australian Government	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Assuming [redacted] scripts per year as estimated by the submission.
Source: As calculated based on figures provided in Section 4 Workshop, tab 3b, 3c and 6.

6.47 The submission estimated that at year six, the number of patients would be less than 10,000 and the net cost to PBS would be more than $100 million per year (a total of substantially more than $100 million over the first six years of listing). The PSCR (p.4) presented revised financial estimates incorporating a change to the eligible population due to the updated restriction criteria, which reduced the overall financial impact to the PBS to substantially more than $100 million over the first six years of listing.

6.48 The DUSC considered that the PSCR estimates were likely to be overestimated, as:

- The assumption for the annual growth in the eligible population ([redacted]%) was a likely overestimate. It was based on the uptake of letrozole that is used to treat a wider range of cancers than ribociclib.
- The uptake rate of [redacted]% 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.
- The estimate of the number of prescriptions per patient per year ([redacted]) was uncertain as it was based on interim results for the mean relative dose intensity from the MONALESSA-2 trial. The dose intensity in practice may differ to that observed in the clinical trial.
- 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.
- There is a risk of continued use of ribociclib following disease progression as the continuation criteria is not based on an objective measure.
- Additional medicine costs to treat adverse events associated with ribociclib were not included.

6.49 The Pre-PBAC response (p.4) reiterated that the financial estimates for ribociclib assumed palbociclib was not reimbursed and therefore constituted the whole CDK 4/6 inhibitor market, in the event that palbociclib was accepted for reimbursement on a cost minimisation basis to ribociclib (or vice versa).

6.50 [redacted] but noted that the final number of grandfathered patients will depend on [redacted]

6.51 The pre-PBAC response presented revised financial estimates that incorporated:

- an updated annual growth of the eligible population ([redacted]%) to more closely align with lowest rate of growth (i.e., [redacted]%) recorded for letrozole based on the last full 5 years of PBS data;

- amended uptake rates of [redacted]% in Year 1, [redacted]% in Year 2, [redacted]% in Year 3 and [redacted]% from Years 4-6, citing a review of the IPSOS data which indicated that approximately [redacted]% of patients currently receiving hormone therapy for ABC began therapy within the last 12 months; and
- an estimated [redacted] additional patients from [redacted] ribociclib in the first year of listing.

The pre-PBAC response claimed that the updated total cost to the Commonwealth at the proposed effective price was $60 – $100 million in the Year 1 listing, increasing to more than $100 million per year in Year 6 (total of substantially more than $100 million in the first six years). The pre-PBAC response noted that this represented a reduction of more than [redacted]% in the first year of PBS listing (previously more than $100 million) for CDK inhibitors and approximately [redacted]% over the first six years of listing (substantially more than $100 million). These estimates were not independently evaluated.

Quality Use of Medicines

6.52 Ribociclib is taken at a dose of 600 mg on days 1-21 of a 28-day cycle. There is a risk of accidental continuation, as some patients may not realise that they need to take a week off treatment. However, the DUSC considered that the target population would be subject to intense monitoring and there would be other opportunities to advise patients on the use of their medicines in addition to the point of dispensing.

Financial Management – Risk Sharing Arrangements

6.53 The submission included a request for a Special Pricing Arrangement for ribociclib, with a [redacted]% rebate on the published prices. The submission did not propose a Risk Share Arrangement.

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 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. The PBAC considered that the ICER was unacceptably high, noting that this was largely driven by the cost of ribociclib. The PBAC considered that although ribociclib treatment resulted in slower disease progression, this was not associated with better quality of life or proven improvement in overall survival, and the addition of ribociclib resulted in a significant increase in treatment-related toxicity. Additionally, the PBAC considered that the likely net cost of listing ribociclib on the PBS would be substantially more than $100 million per year (at the proposed effective price) over the first six years, and as such, there would be a significant opportunity cost to the Commonwealth. The PBAC further noted 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.

7.2 The PBAC welcomed the comments received via the Consumer Comments facility on the PBS website. The PBAC noted that breast cancer is the most common form of cancer in women and that the majority of patients with ABC have the HR+ / HER2- type (approximately 70% based on advice from the DUSC in its consideration of palbociclib (paragraph 7.15, March 2017 PSD)). The PBAC noted that although second-line everolimus and chemotherapy are toxic in the proposed PBS population, first-line endocrine therapy alone is effective in most women with minimal toxicity. As such, the PBAC was concerned that, like palbociclib, ribociclib's currently reported efficacy (without demonstrated OS benefit) and harms had not yet identified the patient population who would gain most benefit nor justified the approach to estimating the cost-effectiveness of this treatment on the PBS, at the price proposed by the sponsor. The PBAC noted an editorial by AC Wolff in the New England Journal of Medicine (2016; 375:1993) which concluded: "CDK4 and CDK6 inhibition in combination with antiestrogens is clearly a new standard for the treatment of advanced ER-positive breast cancer. However, palbociclib is costly and has some toxic effects. Some patients derive strong clinical benefit with antiestrogens alone as first-line therapy, and we must learn to identify those patients so that we can apply CDK4 and CDK6 inhibition in those who will benefit the most."

7.3 The PBAC agreed with its subcommittees that 'advanced breast cancer' may be interpreted differently between clinicians, and that a clearer definition of the population for subsidised treatment would be appropriate to avoid leakage into a broader population. The PBAC also noted DUSC's concerns regarding access to stage III patients without inoperable disease. The PBAC therefore advised that "inoperable stage IIIB/IIIC (locally advanced) or stage IV (metastatic) breast cancer" or "locally advanced inoperable and metastatic breast cancer" be used as PBS indications for ribociclib.

7.4 The PBAC considered that the restriction for ribociclib should allow for it to be prescribed in combination with any NSAI, i.e. anastrozole and letrozole. The PBAC considered that the proposal in the pre-PBAC response to include a continuation criterion based on RECIST may be appropriate.

7.5 The PBAC noted its subcommittees' and the sponsor's proposals for several restriction criteria that would result in better alignment with the inclusion criteria of the MONALEESA-2 trial, and considered that the PBS restriction for ribociclib should exclude the following patient subgroups:

- Patients with a ECOG performance status of 2 or more;
- those with >28 days of treatment with an NSAI for their ABC prior to initiation of ribociclib;
- those with 'inflammatory breast cancer' or 'uncontrolled brain metastases';

- pre-menopausal women receiving treatment with a luteinizing hormone-releasing hormone agonist (LHRHa) (goserelin acetate or leuprolide acetate); and

7.6 The PBAC considered that the criterion 'Patient must not be pre-menopausal' was appropriate. The PBAC also recalled its previous recommendation in November 2014 to extend eligibility for several breast cancer medicines to male patients, on equity grounds.

7.7 The PBAC considered that an initial written authority with a signed patient acknowledgement form, followed by telephone authority for continuing treatment, was reasonable.

7.8 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.

7.9 The PBAC noted that the 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). 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 [redacted] 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.

7.10 The PBAC noted the PSCR's (p.1) argument that PBAC recommendations based on a trend towards improved OS are not without precedent, noting the March 2002 PBAC recommendation for first-line use of letrozole in patients with ABC based on acceptable cost-effectiveness compared with tamoxifen. The PBAC considered that while the letrozole recommendation was a relevant precedent, the uncertainty in the OS outcome was considered in the context of the estimate of cost effectiveness on which the recommendation was based ($[redacted] per life year gained).

7.11 The PBAC noted the high rate of AEs associated with ribociclib, with the majority of patients in the ribociclib + letrozole arm of the MONALEESA-2 trial experienced Grade≥3 AEs ([redacted]%, compared with [redacted]% for letrozole alone). The PBAC

considered that the high incidence of neutropenia was manageable in clinical practice via dose reductions. However, the PBAC noted that ribociclib treatment resulted in substantially higher instances of hepatobiliary toxicity (24.0% ribociclib + letrozole versus 13.6% letrozole alone) and inducement of QT interval prolongation (7.5% ribociclib + letrozole versus 2.4% letrozole alone). The PBAC therefore advised that the submission's claim of inferior safety compared with letrozole alone was reasonable.

7.12 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 more 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.

7.13 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. 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) 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.

7.14 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.

7.15 The PBAC noted that the overall financial impact of ribociclib to the PBS was over substantially more than $100 million per year over the next six years, based on the financial estimates presented in the submission. The PBAC considered that the financial estimates presented in the submission were overestimated, on account of several inappropriate assumptions as identified by DUSC (see paragraph 6.48). The PBAC noted that the pre-PBAC response (p.4) presented revised estimates, which reduced the financial impact to substantially more than $100 million per year in the first six years of listing, but that these estimates have not been evaluated.

7.16 Overall, the PBAC noted that there was significant opportunity cost of listing ribociclib, particularly in the context of the uncertainty of cost-effectiveness driven by immature the survival data. In this regard, the PBAC considered that a tight

subsidisation cap through an RSA would be important if ribociclib were recommended for listing.

7.17 The PBAC noted that the sponsor intended to lodge a major resubmission for ribociclib for consideration by the Committee at its November 2017 meeting. The PBAC considered that the resubmission should address the following (while noting that the resubmission will have been lodged before the sponsor receives this advice):

- An updated set of restriction criteria reflecting PBAC's recommendations (see paragraph 7.3 to 7.7);
- Any further evidence that may be available to demonstrate the comparative efficacy and safety of ribociclib in the proposed PBS population to compensate for the lack of evidence regarding the comparative survival benefit (prior to when this data is expected to become available in 2020);
- The economic model updated with the latest interim data analysis for evaluation and a time horizon for the economic model of no more than 5 years, given the lack of evidence of the effect of ribociclib on survival;
- Amended utilisation estimates reflecting the updated restriction criteria; and
- An RSA to account for the uncertainty in treatment duration and the risk of use beyond progression.

7.18 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.

7.19 The pre-PBAC response (p.1) acknowledged the immature nature of the evidence presented, and proposed that the absence of mature OS data be mitigated by an alternative arrangement, such as a review at the time of availability of OS data. 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.

7.20 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

The sponsor had no comment.