

6.10 RIBOCICLIB, Tablet 200 mg, Kisqali[®], NOVARTIS PHARMACEUTICALS AUSTRALIA PTY LIMITED

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required (telephone/online) listing for ribociclib in combination with adjuvant endocrine therapy (ET) for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), axillary lymph node positive, invasive, resected early breast cancer (eBC) at high risk of disease recurrence.
- 1.2 The submission claimed non-inferior efficacy and safety against abemaciclib plus adjuvant ET and presented a cost-minimisation approach (CMA) versus abemaciclib plus adjuvant ET in support of its claim. The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	Adult patients with HR-positive, HER2-negative, stage II and III eBC with 1-3 positive ALNs and a tumour size \geq 5 cm or histological grade 3 (on the Nottingham grading system), or \geq least 4 positive ALNs
Intervention	Ribociclib, 400 mg orally once daily on days 1-21 of each 28-day cycle for up to 3 years, + adjuvant ET
Comparator	Abemaciclib, 150 mg orally twice daily for up to 2 years, + adjuvant ET
Outcomes	iDFS, DRFS and OS
Clinical claim	Ribociclib + adjuvant ET is noninferior to abemaciclib + adjuvant ET with respect to efficacy and safety

Source: Table 1.1-1, p2 of the submission.

ALN = axillary lymph node; DRFS = distant recurrence-free survival; eBC = early breast cancer; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; iDFS = invasive disease-free survival; OS = overall survival.

2 Background

Registration status

- 2.1 The submission was made under the Therapeutic Goods Administration/ Pharmaceutical Benefits Advisory Committee (TGA/PBAC) Parallel Process. A positive TGA Delegate's Overview was received on 5 November 2024; the Delegate proposed to approve ribociclib for registration in early breast cancer.
- 2.2 The indication proposed for ribociclib in eBC in the draft Product Information (PI), and considered in the Delegate's Overview, was '... for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2

(HER2)-negative stage II and III early breast cancer, in combination with an aromatase inhibitor’.

Previous PBAC consideration

- 2.3 Abemaciclib is currently subsidised on the PBS for the treatment of HR+, HER2-, lymph node positive, invasive, resected eBC at high risk of disease recurrence. The listing was recommended by the PBAC based on a cost-effectiveness analysis comparing abemaciclib plus adjuvant ET versus ET alone (paragraph 7.1, abemaciclib Public Summary Document (PSD), March 2023).
- 2.4 Ribociclib is currently PBS listed for use in combination with either a non-steroidal aromatase inhibitor (AI) (if never treated with prior endocrine therapy) or fulvestrant (250 mg/5 mL injection) for the treatment of patients with HR+, HER2- advanced or metastatic breast cancer.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No.of Rpts	Available brands
RIBOCICLIB					
Ribociclib 200 mg, tablet, 21	\$2,016.02 ^a published price \$TBD effective price	1	21	5	Kisqali Novartis Pharmaceuticals Australia Pty Ltd
Ribociclib 200 mg, tablet, 42	\$3,878.24 ^a published price \$TBD effective price	1	42	5	

AEMP = Approved ex-manufacturer price; CMA= cost minimisation approach; TBD = to be determined.

^a DPMQ were corrected during the evaluation based on the AEMP derived in the CMA.

Category / Program: General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Indication: Early breast cancer
Clinical criteria
The treatment must be adjuvant to surgical resection
AND
The condition must not have been treated with adjuvant endocrine therapy for more than 12 months prior to commencing this drug
AND
The condition must be human epidermal growth factor receptor 2 (HER2) negative
AND
The condition must be hormone receptor positive
AND
The condition must be at high risk of recurrence at treatment initiation with this drug, with high risk being any of: (a) cancer cells in at least 4 positive axillary lymph nodes, (b) cancer cells in 1 to 3 positive axillary lymph nodes plus at least one of: (i) tumour size of at least 5 cm in size, (ii) grade 3 tumour histology (on the Nottingham grading system)
AND
The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) a total of 3.00 years of active treatment (this includes any non-PBS subsidised supply if applicable), (ii) disease recurrence/progression

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AND
The treatment must not be in combination with (i) abemaciclib, (ii) olaparib, (iii) pembrolizumab
AND
Treatment criteria:
Patient must be undergoing concurrent treatment with a non-steroidal aromatase inhibitor where this drug is being prescribed as a PBS-benefit
Prescribing Instructions: Retain all pathology imaging and investigative test results in the patient's medical records.
Administrative Advice: Non-steroidal aromatase inhibitors for the purposes of this restriction are anastrozole and letrozole.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Caution: QT interval monitoring is required for patients treated with this drug.

Source table 1.4-2, pp43-44 of the submission.

cm = centimetre, HER2 = human epidermal growth factor receptor 2, PBS = Pharmaceutical Benefits Scheme.

- 3.1 In addition to the requested listing, the submission proposed an amended listing for ribociclib for HR+, HER2-, inoperable, locally advanced or metastatic breast cancer (not shown here). The amended listing is discussed below (see paragraph 3.6).
- 3.2 The evaluation corrected the submission's proposed published dispensed price for maximum quantity (DPMQ) based on the AEMP. The corrected DPMQ is \$2,016.02 per pack of 21 tablets, and \$3,878.24 for the pack of 42 tablets. The submission did not propose an effective price, noting that the comparator abemaciclib has a Special Pricing Arrangement (SPA); the sponsor indicated their intent for the SPA for ribociclib to be based on the CMA.
- 3.3 The requested restriction was consistent with the evidence presented in the submission and the existing PBS listing for abemaciclib, with the exception that:
 - it excluded tamoxifen (an anti-oestrogen that may be used in men and both pre- and post-menopausal women) as a possible ET, due to a potential increased risk of QT prolongation when co-administered with ribociclib;
 - it requested a longer time (12 months compared to 6 months) between initiation of adjuvant ET and ribociclib; and
 - it did not include a requirement for treatment with CDK4/6 inhibitors to be restricted to one line of therapy at any disease staging for breast cancer (see paragraph 3.6 below).
- 3.4 The evaluation noted that the proposed PBS listing was narrower than the requested TGA indication, which does not refer to lymph node or high-risk status of the disease.
- 3.5 In requesting a 12-month window between commencement of ET and ribociclib on the PBS, the submission argued that the NATALEE trial allowed randomisation to ribociclib within 12 months of prior ET. The submission stated this longer window,

compared with the 6-month window applied to abemaciclib, allows clinicians more flexibility in planning and adjusting treatment schedules based on the patient's initial response to ET, their overall health status, and potential side effects. The evaluation noted that:

- the mean time to initiate treatment in the intention to treat (ITT) population in the NATALEE trial was only 3.5 months (SD: 2.84 months);
- the ESC previously noted that the requirement for patients to have been treated with ET for no longer than 6 months prior to the initiation of abemaciclib was to minimise the risk of use of abemaciclib in a population for which the cost-effectiveness had not been determined (paragraph 3.3, abemaciclib PSD, November 2023).

The Pre-Sub-Committee Response (PSCR) stated that aligning the ribociclib restriction with that for abemaciclib does not align with the clinical evidence for ribociclib, as 21.5% of patients in the NATALEE trial commenced ET >6 months prior to randomisation. The pre-PBAC response further stated that ribociclib patients in NATALEE had similar outcomes whether they started ribociclib < 6 months or > 6 months after starting ET and flexibility of timing is important for patients who have had breast reconstruction or have experienced complications following surgery. However, the ESC and the PBAC did not consider the clinical evidence supported waiting more than 6 months to start ribociclib as an adjuvant therapy and noted that 49.4% of patients in the NATALEE trial commenced ET ≤ 6 months prior to randomisation. Further, the PBAC considered that in the context of eBC at high risk of recurrence, there is a clinical imperative to start therapy with a CDK4/6 inhibitor within 6 months of starting ET. The PBAC noted that an interval of 12 months may have been appropriate in the context of recruiting patients for a clinical trial, but it would not be appropriate in a real-world setting.

3.6 The PBS restriction for abemaciclib in eBC states: “PBS-subsidised treatment with CDK 4/6 inhibitors is restricted to one line of therapy at any disease staging for breast cancer (i.e. if therapy has been prescribed for early disease, subsidy under locally advanced or metastatic disease is no longer available).” The PBS restrictions for abemaciclib and ribociclib in locally advanced or metastatic BC have the same statement. The submission omitted including this requirement in the requested restriction for ribociclib in eBC, and furthermore proposed removing it in the advanced/metastatic setting to allow re-treatment with ribociclib. The submission provided the following arguments to justify this change:

- Evidence from the postMONARCH trial (Kalinsky et al., 2024)¹, a double-blind, placebo-controlled clinical trial that enrolled patients who either relapsed on a

¹ Kalinsky K et al, 2024. Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on a prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the phase 3 postMONARCH trial. *Journal of Clinical Oncology*, 42, LBA1001-LBA1001.

CDK4/6 inhibitor plus adjuvant ET for eBC, or who had disease progression on a CDK4/6 inhibitor plus an aromatase inhibitor (AI) as first-line treatment for advanced breast cancer, showed that patients who received abemaciclib plus fulvestrant following disease progression on prior CDK4/6 inhibitor plus adjuvant ET had a statistically significant 34% lower risk of disease progression or death compared to those treated with placebo plus fulvestrant ($p = 0.01$). The evaluation noted that results from the postMONARCH trial do not support removing the one line of therapy restriction because patients in both the abemaciclib and placebo arms had already received treatment with a CDK4/6 inhibitor.

- The ESMO and NCCN guidelines recommend re-treatment with CDK4/6 inhibitors in the advanced setting, given enough time has elapsed since disease progression (ESMO, 2023; NCCN, 2023). In particular, the ESMO (2021) guidelines state that ‘Although there is little data on use of CDK4/6 inhibitors after progression on CDK4/6 inhibitors, rechallenge may be possible after a treatment-free interval of ≥ 12 months based on evidence regarding rechallenge with other therapies’ (Gennari et al., 2021).
- According to advice provided from Australian clinicians experienced in the treatment of breast cancer, it is appropriate for patients with HR+, HER2- breast cancer who relapsed after adjuvant treatment with ribociclib plus adjuvant ET, to be re-treated with ribociclib (or another CDK4/6 inhibitor) in the advanced setting (for patients who relapsed at least 12 months after completing adjuvant treatment). The evaluation noted that the submission did not provide any additional details or evidence regarding this advice to support the change in restriction in the advanced setting.

3.7 The ESC did not support removal of the one line of therapy restriction criterion for CDK4/6 inhibitors. The ESC noted that:

- In the NATALEE trial, only 37/2,524 (1.5%) patients received a CDK4/6 inhibitor as a post-treatment anti-cancer therapy: abemaciclib (0.8%), palbociclib (0.5%), ribociclib (0.3%), ribociclib succinate (only 1 patient).
- The NATALEE Clinical Study Report (CSR) did not specify if these patients were metastatic at the time they received subsequent treatment with a CDK4/6 inhibitor.
- The PBAC previously stated there were no safety or efficacy data for sequential use of CDK4/6 inhibitors (see paragraph 5.3 below), and no further evidence was provided.

The PBAC further noted that only 1% of the patients in the postMONARCH study had received prior adjuvant CDK4/6 inhibitor treatment (as opposed to prior CDK4/6 inhibitor treatment for metastatic BC)².

- 3.8 The PBAC noted that the requested restriction would allow patients to switch to ribociclib after being treated for early breast cancer with another CDK4/6 inhibitor (and vice versa). The PBAC considered that patients should be able to switch between the CDK4/6 inhibitors for eBC before disease progression, noting the alternative ribociclib and abemaciclib safety profiles (see paragraph 6.45 below), and that this should be permitted only if patients experience intolerance of a severity necessitating permanent treatment withdrawal.

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

4 Population and disease

- 4.1 Ribociclib was proposed to be considered as an alternative CDK4/6 inhibitor to abemaciclib in adult patients with HR+, HER2-, lymph node positive, invasive, resected, eBC at high risk of recurrence.
- 4.2 The most common cancer type in women in Australia is breast cancer, which also accounts for the second most common cause of cancer related death. In 2019, there were 18,659 newly diagnosed breast cancer patients, equivalent to an age-standardised incidence rate of 76.7 cases per 100,000 people (AIHW, 2023). Most of these cancers are diagnosed at an early stage (95%) and most are HR+ and HER2- accounting for about 70% of cases. Evidence suggests the annualised hazard of recurrence was highest during the first 5 years (10.4%), with a peak between years 1 and 2 (15.2%)³.
- 4.3 Ribociclib is an orally bioavailable and highly selective small molecule inhibitor of the CDK 4/6 enzyme complex, which directly targets the retinoblastoma protein to block cell cycle progression and cancer cell proliferation.
- 4.4 The proposed use of ribociclib is in combination with ET (letrozole or anastrozole). In men and pre-menopausal women, ET is ineffective unless administered with ovarian suppression (e.g., goserelin or triptorelin); in the NATALEE trial, patients were given goserelin, administered as a 3.6 mg subcutaneous implant once every 28 days. Patients may have had neoadjuvant or adjuvant radiotherapy and/or chemotherapy prior to ribociclib plus adjuvant ET.

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

² Kalinsky K et al, 2024. Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on a prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the phase 3 postMONARCH trial. *Journal of Clinical Oncology*, 42, LBA1001-LBA1001.

³ Colleoni M, Sun Z, Price KN, Karlsson P, Forbes JF, Thürlimann B, Gianni L, Castiglione M, Gelber RD, Coates AS, Goldhirsch A. Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V. *J Clin Oncol*. 2016 Mar 20;34(9):927-35.

5 Comparator

- 5.1 The submission nominated abemaciclib plus adjuvant ET as the comparator. The ET component in the comparator consists of AIs (i.e., letrozole, anastrozole or exemestane) or oestrogen receptor modulator (tamoxifen). The PBAC agreed with the evaluation and the ESC that the choice of comparator was appropriate.
- 5.2 Ribociclib will replace some of the use of abemaciclib in the eBC setting. In contrast to the proposed restriction for ribociclib in eBC, the current restriction of abemaciclib in eBC does not allow for sequential use (see paragraph 3.3). Sequential use of CDK4/6 inhibitors was not captured in the NATALEE trial and was not considered in the economic analysis and financial estimates.
- 5.3 The evaluation noted that when abemaciclib was being considered for PBS listing in the eBC setting, the PBAC stated that flow on changes to all CDK4/6 inhibitors currently PBS listed in the advanced/metastatic treatment setting would be required to exclude sequential use (i.e., use in eBC and then use in advanced/metastatic breast cancer) as there are currently no safety or efficacy data for repeated use of CDK4/6 inhibitors (paragraph 7.4, abemaciclib PSD, November 2023). The restrictions for abemaciclib, palbociclib and ribociclib were subsequently updated to limit subsidy to one line of therapy for a CDK4/6 inhibitor, irrespective of whether prescribed for early or late-stage disease (as discussed in paragraph 3.6 with respect to the requested restriction).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed the benefits of having an alternative CDK4/6 inhibitor as a treatment option for eBC patients. The clinician advocated allowing a 12-month window after starting ET to initiate ribociclib and claimed that prior exposure with CDK4/6 inhibitors in eBC is favourable to treating advanced/metastatic disease with CDK4/6 inhibitors.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from 5 organisations via the Consumer Comments facility on the PBS website. The organisations (Medical Oncology Group of Australia [MOGA], Rare Cancers Australia, Inherited Cancers Australia [formerly Pink Hope], Can Assist, and Breast Cancer Network Australia [BCNA]) supported the PBS listing of ribociclib for the treatment of HR+, HER2- lymph node positive, invasive resected eBC. The organisations outlined the clinical benefits associated with ribociclib treatment as an alternative CDK4/6 inhibitor, especially for patients unable to tolerate currently listed medicines, and emphasised the psycho-social benefits associated with reducing the fear of recurrence.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the ribociclib submission, categorising it as one of the therapies of “high priority for PBS listing” on the basis of the NATALEE trial. The PBAC noted that the MOGA classified ribociclib with a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) grade ‘B’, categorising it as a treatment with substantial benefit in the curative setting.⁴

Clinical trials

6.4 The submission was based on an anchored indirect treatment comparison (ITC) of ribociclib plus adjuvant ET and abemaciclib plus adjuvant ET, using ET alone as the common reference. The submission’s ITC was based on two randomised trials: NATALEE comparing ribociclib plus adjuvant ET to ET alone (N=5,101), and monarchE comparing abemaciclib plus adjuvant ET to ET alone (N=5,637).

6.5 Details of the two trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
NATALEE (NCT03701334)	A phase III, multicenter, randomised, open-label trial to evaluate efficacy and safety of Ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer (New Adjuvant Trial with Ribociclib [LEE011])	CSR; DCO: 11 January 2023 Report: 2 August 2023
	A phase III, multicenter, randomised, open-label trial to evaluate efficacy and safety of Ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer: efficacy analysis and safety update Final iDFS Analysis	Clinical Trial Protocol DCO: 21 July 2023 Report: 23 November 2023
	Slamon et al. Ribociclib plus Endocrine Therapy in Early Breast Cancer.	<i>NEJM</i> 2024; 390:1080-1091
	Slamon et al. Rationale and trial design of NATALEE: a Phase III trial of adjuvant ribociclib + endocrine therapy versus endocrine therapy alone in patients with HR+/HER2- early breast cancer.	<i>Ther Adv Med Oncol</i> , 15
monarchE (NCT03155997)	Johnston et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE).	<i>Journal of clinical oncology</i> 2020; 38:3987-3998.
	Harbeck et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study.	<i>Annals of Oncology</i> 2012; 32:1571-1581.
	Johnston et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial.	<i>The Lancet Oncology</i> 2023; 24:77-90.
	A Randomized, Open-Label, Phase 3 Study of Abemaciclib Combined with Standard Adjuvant Endocrine Therapy versus Standard Adjuvant Endocrine Therapy Alone in Patients with High Risk, Node Positive, Early Stage, Hormone Receptor Positive, Human Epidermal Receptor 2 Negative Breast Cancer	Clinical trial protocol. Amendment 18 September 2019

Source: Table 2.2-1, pp60-61 of the submission.

⁴ 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 The key features of the two randomised trials used in the ITC are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Ribociclib plus adjuvant ET vs ET alone					
NATALEE	ITT:5101	R, OL, MC DCO Jan 2023: 34 months DCO July 2023: 40.3 months	Low	HR+, HER2- resected eBC, Stage II or III Regardless of nodal disease	iDFS, DRFS, OS, DDFS, RFS, PROs, safety
Abemaciclib plus adjuvant ET vs ET alone					
monarchE	ITT: 5637 Cohort 1: 5120	R, OL, MC DCO July 2023: 54 months	Low	ITT: HR+, HER2- resected eBC, Stage II or III, Node 1 was allowed if: 4 ALN+ or 1 to 3 ALN+ with at least one of the following: Grade 3 disease Tumour size ≥ 5 cm Ki-67 index of ≥ 20% Node 0 was not allowed. Cohort 1: as in ITT plus high risk of recurrence: ≥ 4 ALNs; or 1-3 ALNs and tumour ≥ 5cm or grade ≥ 3 disease	iDFS, DRFS, OS, safety

Source: Compiled during the evaluation; Table 2.2-1 pp60-61, Table 2.2.-2 p63 and Table 2.3-1, pp68-69 of the submission.
ALN = axillary lymph node; DCO = data cut-off; DRFS = distant recurrence-free survival; eBC = early breast cancer; ET = endocrine therapy;
HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; iDFS = invasive disease-free survival; ITT
= intention to treat; MC = multi-centre; OL = open label; OS = overall survival; R = randomised.

6.7 The submission relied on data from the subgroup of patients in the NATALEE trial with stage II and III eBC at a high-risk of recurrence defined as ≥4 positive axillary lymph nodes (ALNs), or 1-3 positive ALNs and either grade 3 disease or tumour size ≥ 5 cm. This subgroup (hereafter referred to as ‘PBS subgroup’) was not pre-specified and comprised 65% of the NATALEE trial ITT population. The PBAC previously recommended the listing of abemaciclib on the PBS for the same population, based on the clinical efficacy and safety from the evidence presented for the monarchE trial subgroup (Cohort 1) population (paragraph 6.10, abemaciclib PSD, March 2023). The Cohort 1 subgroup of the monarchE trial was pre-specified and corresponded to 91% of the ITT population.

6.8 The evaluation noted that the use of tamoxifen differed between the trials. In the NATALEE trial, patients were not allowed to receive ribociclib in combination with tamoxifen as adjuvant ET, as it is contraindicated due to increased risk of prolonged QT. In the monarchE trial, 31.4% patients in the safety population and 31.1% in the ITT population received tamoxifen as adjuvant ET. To account for this difference between

the trials, the submission also presented comparisons using an adjuvant AI subgroup from monarchE that excluded the results from patients receiving tamoxifen (this subgroup was pre-specified).

6.9 Different subgroups of the NATALEE and monarchE trials informed the efficacy results as summarised in Table 4.

Table 4: Subgroups of patients that inform the efficacy and safety data in the ITC

	Abemaciclib (monarchE trial)				Ribociclib (NATALEE trial)			
	ITT	Cohort 1 (PBS population) subgroup	Adjuvant AI subgroup (exclude tamoxifen)	Safety set	ITT	PBS population subgroup	Safety Set	Safety set (monarchE ITT eligible) subgroup
Patient's baseline characteristics available?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Number of patients in the intervention arm N (% of ITT)	2,808 (100%)	2,555 (91%)	1,931 (68.8%)	2791 (99.4%)	2,549 (100%)	1,659 (65.1%)	2,525 (99.1%)	1,888 (74.2%)
Indirect treatment comparison								
Primary analysis			X			X		
Supportive analysis		X				X		
ITC safety				X				X

Source: developed during the evaluation.

AI= aromatase inhibitor; CMA= cost minimisation approach; ITC = Indirect treatment comparison; ITT= intention to treat; PBS = Pharmaceutical Benefits Scheme.

Note that the results presented in Table 4 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.10 Given the differences in the adjuvant ET accompanying each CDK4/6 inhibitor, the submission's primary ITC analysis was between the NATALEE PBS subgroup and a subgroup of patients in the monarchE trial that used adjuvant AI (monarchE ITT population excluding patients treated with tamoxifen, hereafter referred to as 'adjuvant AI subgroup'). The ITC analysis comparing the NATALEE PBS subgroup with Cohort 1 subgroup from monarchE was nominated as supporting evidence. The evaluation noted that the submission's nominated primary comparison in the ITC compared the requested PBS population from NATALEE with an abemaciclib patient population that may not reflect the currently listed abemaciclib PBS population, and made the following points regarding this comparison:

- the submission did not provide the baseline characteristics of these abemaciclib patients in monarchE; therefore, it is unknown whether this population reflects the PBS population.
- the submission compared the common reference arms (ET alone) for the outcomes invasive disease-free survival (iDFS) and disease recurrence-free survival (DRFS) of the nominated PBS subgroup in NATALEE and Cohort 1 in

monarchE, and showed the ET arms entirely overlap, suggesting that the comparator arms from both trials perform similarly.

- The abemaciclib subgroup analysis included in the submission showed that the type of first ET (tamoxifen or AI) in monarchE was not a treatment effect modifier.

6.11 The submission based its clinical claim on the primary outcomes of invasive disease-free survival (iDFS) and secondary outcome distant recurrence-free survival (DRFS). Overall survival (OS) was also assessed as a secondary outcome in both trials but was not included in the clinical claim because of the small number of deaths in the clinical trials. The evaluation noted that the PBAC previously stated that due to immature OS data in monarchE, there remained an unclear relationship between iDFS/DRFS and OS (paragraph 7.7, abemaciclib PSD, November 2023).

6.12 The safety ITC was based on a safety set of monarchE and NATALEE (monarchE ITT eligible) population, with no ITC presented for the PBS-eligible subgroup used in the ITC of efficacy data.

Comparative effectiveness

Ribociclib plus adjuvant ET versus ET alone (NATALEE trial)

6.13 Table 5 summarises the results for iDFS, DRFS and OS for NATALEE (ITT and PBS subgroup) population. The results for the key outcomes of iDFS and DRFS indicate statistically significant benefit for ribociclib plus adjuvant ET compared to ET alone in the ITT population and PBS subgroup.

Table 5: Summary of survival outcomes in NATALEE (ITT and PBS subgroup, DCO July 2023)

Outcome	Ribociclib plus adjuvant ET n/N (%)	ET alone n/N (%)	HR (95% CI)
iDFS			
ITT	226/2549 (8.9%)	283/2552 (11.1%)	0.749 (0.628; 0.892); p = 0.0006
PBS subgroup	177/1659 (10.7%)	218/1649 (13.2%)	0.744 (0.609, 0.908); p = 0.002
DRFS			
ITT	178/2549 (7.0%)	227/2552 (8.9%)	0.738 (0.606, 0.898); p = 0.0012
PBS subgroup	145/1659 (8.7%)	181/1649 (11.0%)	0.735 (0.590, 0.916); p = 0.003
OS			
ITT	84/2549 (3.3%)	88/2552 (3.4%)	0.892 (0.661, 1.203); p = 0.2263
PBS subgroup	69/1659 (4.2%)	71/1649 (4.3%)	0.917 (0.658, 1.280); p = 0.306

Source: Table 2.5-1, p94, Table 2.5-7, p106, Table 2.5-6 p104, Table 2.6-6, p131 of the submission.

CI = confidence interval; DCO = data cut-off; DRFS = distant recurrence-free survival; ET = Endocrine therapy; FAS = full analysis set; HR = hazard ratio; iDFS = Invasive disease-free survival; ITT = intention to treat; KM = Kaplan-Meier; n = number of participants with event; N = total participants in group; NE = not estimable; OS = overall survival; PBS= Pharmaceutical Benefit Scheme.

Bold indicates statistically significant results.

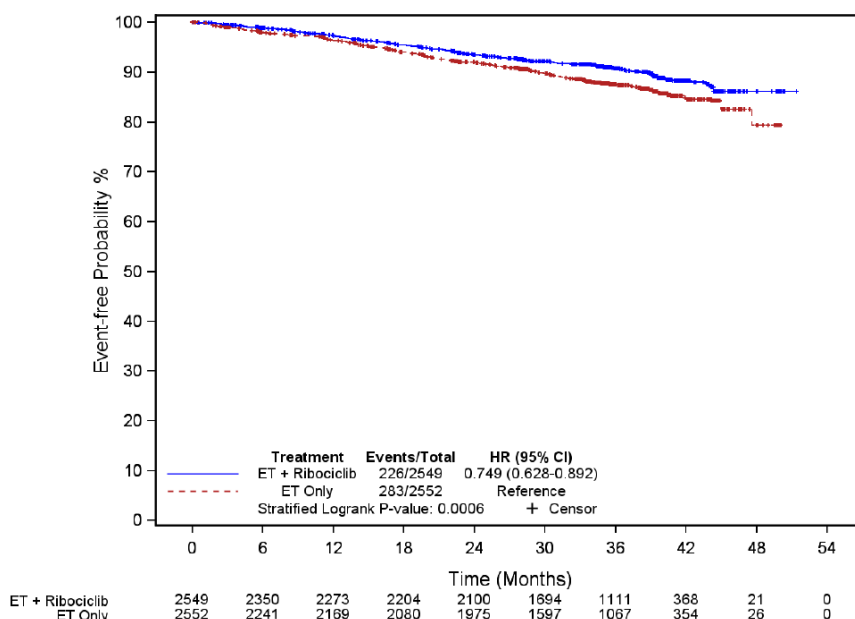
Note that the results presented in Table 5 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.14 In the ITT population, with a median follow-up of 40.3 months (data cut-off (DCO) July 2023), ribociclib plus adjuvant ET showed a 25.1% relative reduction in the hazard

of invasive disease recurrence, as evidenced by a HR of 0.75 (95%CI: 0.63; 0.89; $p = 0.0006$) for iDFS and a 26.2% relative reduction in the hazard of distant disease recurrence with a hazard ratio (HR) of 0.74 (95%CI: 0.61, 0.90; $p = 0.0012$) for DRFS. The risk reduction was similar in the PBS subgroup, with a HR of 0.74 (95%CI: 0.61, 0.91; $p = 0.002$) for iDFS and a HR of 0.74 (95%CI: 0.59, 0.92; $p = 0.003$) for DRFS⁵. The evaluation noted that ribociclib offers a benefit that is not worse in the PBS subgroup population compared to the ITT population.

- 6.15 The Kaplan-Meier (KM) curves for the primary outcome, iDFS for the ITT population and PBS subgroup in NATALEE are presented in Figures 1 and 2 respectively. The curves start to diverge at around 30 months, noting that there appears to be heavy censoring post Month 36 (the ITT KM shows a drop from ~1100 to ~350 patients at risk at Month 42, and then only ~20 patients remain at risk by Month 48).
- 6.16 The results for OS showed no significant difference between the two arms in the ITT population or PBS subgroup population. The submission stated that the small number of deaths in NATALEE is consistent with the prognosis of patients with eBC. The PBAC has previously stated the primary outcome of iDFS is a generally a plausible surrogate for OS in this setting (paragraph 7.8, abemaciclib PSD, March 2022).

Figure 1: KM curves for iDFS at the July 2023 DCO (ITT) in NATALEE

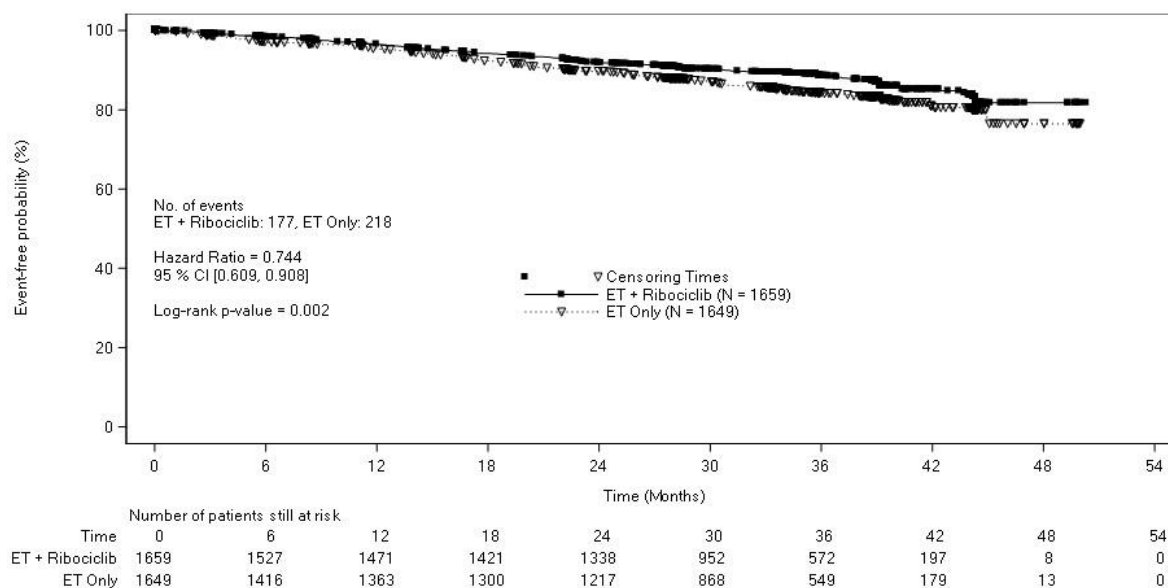


Source: Figure 2.5-1, p96 of the submission.

DCO = Data cut-off; CI = Confidence interval; ET = Endocrine therapy; HR = Hazard ratio; iDFS = Invasive disease-free survival; ITT = intention to treat; KM = Kaplan Meier

⁵ Note that the results presented in paragraph 6.14 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Figure 2: KM curves for iDFS for the nominated PBS population in NATALEE



Source: Figure 2.6-1, p130 of the submission.

ET = endocrine therapy; iDFS = invasive Disease-free survival; KM = Kaplan Meier; PBS = Pharmaceutical Benefit Scheme.

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

Abemaciclib plus adjuvant ET versus ET alone (monarchE trial)

- 6.17 Table 6 summarises the results for primary (iDFS) and secondary outcomes (DRFS and OS) for monarchE ITT, Cohort 1 and adjuvant AI subgroup (ITT population that did not receive tamoxifen). The evaluation noted that the baseline patient characteristics of the adjuvant AI subgroup were not presented in the submission therefore it was uncertain whether this population is representative of the PBS population. The baseline patient characteristics of the ITT population and Cohort 1 were similar.
- 6.18 With a median follow-up of 54 months (DCO July 2023), there was a 32% relative reduction in the hazard of iDFS for abemaciclib plus adjuvant ET compared to ET alone (HR = 0.68; 95% CI: 0.60, 0.77) and a similar result for Cohort 1 (PBS population) with a 33% relative reduction in the hazard of iDFS (HR = 0.67 (95% CI: 0.59, 0.76)).
- 6.19 The submission claimed that the adjuvant AI subgroup of monarchE was the relevant subgroup to compare to the PBS subgroup of NATALEE, as both populations would reflect the same comparator (without tamoxifen as ET). The HR of 0.74 (95%CI: 0.63, 0.86) in the AI subgroup for abemaciclib in the monarchE trial (Table 6) showed a trend towards being less effective compared to the ITT and Cohort 1 subgroup populations (HR 0.68 and 0.67 respectively, paragraph 6.18). The evaluation considered that a comparison of ribociclib plus ET against the abemaciclib plus adjuvant AI subgroup of monarchE could therefore be biased in favour of ribociclib.
- 6.20 The results for DRFS for ITT and Cohort 1 subgroup populations showed a similar trend as in iDFS. The result for OS were presented for ITT and Cohort 1 populations only. The

OS data showed no significant differences between the two arms of the ITT population and Cohort 1 (PBS population) subgroup.

Table 6: Summary of survival outcomes in monarchE (ITT and subgroups)

Events, n (%)	Abemaciclib + ET n with event/N (%)	ET alone n with event/N (%)	Hazard ratio (95%CI)
iDFS			
ITT	407/2808 (14.5)	585/2829 (20.7)	0.680 (0.599, 0.772); p<0.001
Cohort 1 (PBS population)	382/2555 (15)	553/2565 (21.6)	0.670 (0.588, 0.764); p <0.001
Adjuvant AI subgroup*	293/1931 (15.2)	386/1887 (20.5)	0.738 (0.634, 0.859); NR
DRFS			
ITT	345/2808 (12.3)	501/2829 (17.7)	0.675 (0.588, 0.774); p <0.001
Cohort 1 (PBS population)	325/2555 (12.7)	477/2565 (18.6)	0.665 (0.577, 0.765); p <0.001
Adjuvant AI subgroup*	248/1931 (12.8)	330/1887 (17.5)	0.733 (0.622, 0.864); NR
OS			
ITT	208/2808 (7.4)	234/2829 (8.3)	0.903 (0.749, 1.088); p = 0.284
Cohort 1 (PBS population)	197/2555 (7.7)	223/2565 (8.7)	0.894 (0.738, 1.084); p = 0.254

Source: Table 2.6-10, p136, Table 2.6-11 p138, Table 2.6-12 p139 of the submission.

CI = confidence interval; DCO = data cut-off; DCFS = distant recurrence-free survival; ET = endocrine therapy; FAS = full analysis set; HR = hazard ratio; iDFS = invasive disease-free survival; ITT = intention to treat; KM = Kaplan Meier; n = number of participants with event; N = total participants in group; NE = not estimable; OS = overall survival

* Adjuvant AI subgroup of monarchE excluded patients who had received tamoxifen as ET.

Bold indicated statistically significant results.

6.21 The submission presented the results of the patient reported outcomes for the NATALEE trial. Health related quality of life (HRQoL) was assessed as a secondary outcome at the January 2023 DCO using the physical functioning subscale score and the global health status/QoL score of the European Organization for Research and Treatment of Cancer’s Core Quality of Life Questionnaire – C30 (EORTC QLQ-C30).

6.22 The EORTC QLQ-C30 physical functioning and quality of life scores were similar across the treatment arms; and the submission concluded that adding ribociclib to ET treatment does not result in any notable deterioration in HRQoL compared with current standard of care.

ITC Results

6.23 The results of the ITC following the Bucher method are presented in Table 7. The submission noted that the differences between ribociclib and abemaciclib, for the selected key outcomes iDFS and DRFS, were not statistically significant. Therefore, the submission claimed that ribociclib plus adjuvant ET is non-inferior to abemaciclib plus adjuvant ET. The submission did not specify a non-inferiority margin; however, a non-inferiority margin of 1.4 for the upper bound of the 95% CI was presented in previous submissions for abemaciclib and palbociclib in the advanced breast cancer setting (paragraph 7.7, abemaciclib PSD, March 2019; paragraph 5.11, palbociclib PSD, March 2018), noting that the outcome of interest in those submissions was progression free survival (PFS) and not iDFS. The proposed value (1.4) was obtained from a literature review and was specific for eBC (Tanaka, et al 2012), which is the target population in this submission.

- 6.24 The indirect comparisons showed that ribociclib plus adjuvant AI had similar relative clinical benefit compared to abemaciclib plus adjuvant AI with respect to iDFS (HR 1.01, 95% CI: 0.78, 1.30; $p = 0.9496$) and DRFS (HR 1.00, 0.76, 1.32; $p = 0.9845$)⁶. In general, the ITC HRs for all outcomes were close to 1 and in all cases the difference was not found to be statistically significant.
- 6.25 The PSCR presented updated results of the indirect treatment comparison (ITC) based on updated outcomes from NATALEE (PBS subgroup) for iDFS and DRFS. The date of the new DCO and the proportion of patients still on treatment was not stated in the PSCR. The reported HR for iDFS was 0.719 (95%CI: 0.599, 0.862; $p < 0.001$) compared to the reported HR of 0.744 (95%CI: 0.609, 0.908; $p=0.002$)⁶ from the July 2023 DCO presented in submission. Similarly, the updated results for DRFS showed a HR of 0.707 (95%CI: 0.578, 0.864; $p < 0.001$) compared to HR of 0.735 (95%CI: 0.590, 0.916; $p = 0.003$)⁶ from the July 2023 DCO. The PSCR stated that the updated ITC results show that ribociclib is not statistically significantly different to abemaciclib for iDFS and DRFS and that the upper limit of the 95% CIs did not exceed the non-inferiority margin of 1.40. These results should be interpreted with caution given that critical aspects of the updated analysis including patient numbers at risk, date and nature (pre-planned analysis or ad hoc) of the DCO, and corresponding updated safety data were not presented in the PSCR.

⁶ Note that the results presented in paragraphs 6.24 and 6.25 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 7: Bucher indirect comparison of efficacy outcomes for the nominated PBS population

Trial	Comparison	Intervention Events/N (%)	ET alone Events/N (%)	KM estimates at 3 years (absolute difference)	Hazard Ratio (95% CI); p value
iDFS (Primary outcome)					
NATALEE PBS subgroup [^]	RIB+ET vs ET	177/1,659 (10.7)	218/1,649 (13.2)	88.6% vs 84.3% (4.3%)	0.744 (0.609, 0.908); p = 0.002
monarchE adjuvant AI subgroup (excluding tamoxifen as ET)*	ABE+ET vs ET	293/1,931 (15.2)	386/1,887 (20.5)	NR	0.738 (0.634, 0.859); NR
monarchE Cohort 1* (PBS population)	ABE+ET vs ET	382/2,555 (15)	553/2,565 (21.6)	88.9% vs 83.8% (5.1%)	0.670 (0.588, 0.764); p < 0.001
Indirect comparison: RIB+ET vs. ABE+ET (AI subgroup)					1.01 (0.78, 1.30); p = 0.9496
Indirect comparison: RIB+ET vs. ABE+ET (PBS population)					1.11 (0.87, 1.41); p = 0.3899
DRFS (Secondary outcome)					
NATALEE PBS subgroup [^]	RIB+ET vs ET	145/1,659 (8.7)	181/1,649 (11)	90.7% vs 87.2% (3.5%)	0.735 (0.590, 0.916); p = 0.003
monarchE adjuvant AI subgroup (excluding tamoxifen as ET)*	ABE+ET vs ET	248/1,931 (12.8)	330/1,887 (17.5)	NR	0.733 (0.622, 0.864); NR
monarchE Cohort 1* (PBS population)	ABE+ET vs ET	325/2,555 (12.7)	477/2,565 (19.0)	90.5% vs 86.1% (4.4%)	0.665 (0.577, 0.765); p < 0.001
Indirect comparison: RIB+ET vs. ABE+ET (AI subgroup)					1.00 (0.76, 1.32); p = 0.9845
Indirect comparison: RIB+ET vs. ABE+ET (PBS population)					1.11 (0.85, 1.44); p = 0.4528
OS					
NATALEE PBS subgroup [^]	RIB+ET vs ET	69/1,659 (4.2)	71/1,649 (4.3)	95.9% vs 94.9% (1%)	0.917 (0.658, 1.280); p = 0.306
monarchE Cohort 1* (PBS population)	ABE+ET vs ET	197/2,555 (7.7)	223/2,565 (8.7)	Not reported	0.894 (0.738, 1.084); p = 0.254
Indirect comparison: RIB+ET vs. ABE+ET (PBS population)					1.03 (0.70, 1.51); p = 0.8969

Source: Table 2.6-13, p148 of the submission.

ABE = abemaciclib; AI = aromatase inhibitor; CI = confidence interval; DCO = data cut-off; ET = endocrine therapy; ITT = intention to treat; NR = not reported; PBS = Pharmaceutical Benefit Scheme; RIB = ribociclib; iDFS = invasive disease-free survival; DRFS = distant recurrent-free survival; OS = overall survival

* Both Cohort 1 and adjuvant AI subgroups were prespecified.

[^] Post-hoc subgroup

An indirect comparison hazard ratio >1 favours treatment with abemaciclib.

Median follow-up time was 40.3 months for the whole trial population in NATALEE and 54 months for monarchE.

Bold indicates statistically significant difference.

Note that the results presented in Table 7 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.26 The submission presented the results of PBS subgroup in the NATALEE trial versus the adjuvant AI subgroup of the monarchE trial (excluding tamoxifen) as the primary ITC results. However, the patient characteristics for this adjuvant AI subgroup were not presented in the submission; therefore, the evaluation considered that it is uncertain whether this population was representative of the PBS population and that it would

have been more appropriate to present the comparison against Cohort 1 of monarchE as the primary results of the ITC.

6.27 The evaluation noted that the main transitivity concerns identified by the submission were:

- The use of tamoxifen in 31.1% of patients in the ITT population of monarchE. The exclusion of these patients from the ITC introduces a deviation from the population for which listing is being sought. Tamoxifen is part of adjuvant ET used in the Australian target population and is part of the submission's nominated comparator.
- The benefit in terms of iDFS for patients treated with abemaciclib plus adjuvant tamoxifen compared to tamoxifen alone was 43.9% (HR 0.561, 95% CI: 0.445, 0.708), whereas the benefit of treating with abemaciclib plus an AI compared to AI alone was 26.2% (HR 0.738, 95% CI: 0.634, 0.959)⁷. This large shift in the observed HR is consistent with studies showing tamoxifen monotherapy may not be as effective as AI monotherapy in preventing breast cancer recurrence,⁸ however additional confounders and the possibility that randomisation of monarchE may not be preserved in this newly-defined, non-stratified AI subgroup cannot be precluded.
- Difference in the median follow-up time: shorter in the NATALEE trial compared to the monarchE trial (40.3 months vs 54 months). A comparison of the ET common references arms in the nominated PBS populations in NATALEE and monarchE showed that the two curves overlapped, indicating consistency.
- Different treatment durations: the maximum treatment duration for ribociclib (NATALEE) was 3 years compared to 2 years for abemaciclib (monarchE). At the July 2023 DCO, with a median follow up of 40.3 months, 20.7% of patients in NATALEE were still receiving ribociclib. The ESC noted that the sponsor did not provide an update of the median follow-up or the proportion of patients on treatment with ribociclib when updating the ITCs with data from a new DCO in their PSCR. In monarchE all patients had either completed or discontinued the 2-year treatment phase.
- NATALEE safety results are incomplete which may bias the ITC in favour of ribociclib due to patients still being on treatment. ITC in safety was performed

⁷ Note that the results presented in paragraph 6.27 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

⁸ Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015 Oct 3;386(10001):1341-1352.

using a subgroup (74.2%)⁹ of NATALEE aligned to the ITT population of monarchE. The adverse events in the ET only were consistent across the two trials.

Comparative harms

- 6.28 A summary of adverse events (AEs) for ribociclib and abemaciclib is presented in Table 8. The safety outcomes were presented for the safety population for patients in NATALEE who would be eligible for the PBS population (64.9% of NATALEE ITT population) and ITT population of monarchE (72.1% of NATALEE ITT population) and the safety population in monarchE (99% of ITT). Both trials show that ribociclib and abemaciclib have significantly higher rates of AE compared to the ET alone arm. The safety profile of the two subgroup populations from the NATALEE trial are similar to each other and to the NATALEE ITT population.
- 6.29 The treatment phase in NATALEE was aligned with the duration of ET (5 years) and in monarchE the treatment phase was aligned with duration of abemaciclib (2 years). The submission stated that this difference is likely to bias the results for safety against ribociclib given the longer duration.
- 6.30 The discontinuation of treatment due to AEs was reported in 20.8% of patients in the ribociclib plus adjuvant ET arms compared to 5.5% of patients in the ET arms alone¹⁰. The Clinical Evaluation Report (CER) stated the reported 4-fold increase in discontinuation due to AEs compared to ET alone supported the need for close monitoring of AEs¹⁰.
- 6.31 More patients in the NATALEE trial compared to the monarchE trial experienced Grade 3/4 AEs in the treatment arms compared to the ET arms (Table 8). In the NATALEE trial 63.9% of patients in the ribociclib plus ET arm versus 18.9% of patients in the ET alone arm experienced a Grade 3/4 event. In the monarchE trial, 49.9% of patients in the abemaciclib plus ET arm versus 16.9% in the ET alone arm experienced a Grade 3/4 adverse event¹⁰. The risk difference (RD) for ribociclib plus ET versus ET alone was 0.45 (95% CI: 0.42, 0.48) while the RD for abemaciclib plus ET versus was 0.33 (95% CI: 0.31, 0.35)¹⁰. The resulting RD between ribociclib and abemaciclib would be 0.12 noting that the 95% CI do not overlap¹⁰. This result was calculated by the evaluation noting that the study was not powered to detect any difference. Therefore, the evaluation considered that this result should be considered indicative only.

⁹ Note that the results presented in paragraph 6.27 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

¹⁰ Note that the results presented in paragraphs 6.30 and 6.31 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose

- 6.32 The CER noted a 2-fold increase in venous thrombotic and embolic events in the ribociclib plus ET compared to ET alone, 38 versus 19 participants respectively¹¹. Within these patients 18 (0.71%) patients had pulmonary emboli (three events being fatal) compared with 5 events in the ET arm¹¹. The CER also determined that deaths from pulmonary emboli, infection and cardiac events warrant closer inspection to determine if these are chance findings or indicative of a higher risk of death with the addition of ribociclib to ET. The TGA requested the Sponsor present additional data for these adverse events.
- 6.33 The submission reported rates for all deaths in NATALEE and deaths due to treatment emergent adverse event (TEAE) in monarchE. Death was a serious but rare TEAE, with more than twice as many deaths in patients treated with ribociclib plus ET compared to ET alone (20 versus 9, respectively) and a relative risk of 0.00 (95% CI 0.00, 0.01, $p = 0.05$) and odds ratio of 2.16 (95% CI 0.98, 4.75, $p = 0.06$), noting borderline statistical significance¹¹. Comparing the ribociclib plus adjuvant ET arm to the ET alone arm, 6 versus 1 were related to COVID-19/COVID-19 pneumonia; 2 versus 0 were from pulmonary embolisms, 1 versus 0 was a cardiac arrest¹¹. None of the ribociclib deaths were attributed to treatment by the investigators, noting the open label trial design; when considering the number of deaths between the arms of NATALEE, the relative risk p -value of 0.05 suggests it may be unlikely that the increased risk of death in the ribociclib arm was due to chance alone, noting the randomised, large cohort design of the trial. The CER stated 'There was a small but marked increase in early deaths in those receiving ribociclib in addition to ET, and infections and pulmonary emboli were the most common causes'. Furthermore, the CER stated that two deaths occurred after the 30-day window post ribociclib interruption/discontinuation and were not counted as deaths due to TEAE; however, the onset of symptoms and positive SARS-COV-2 test result occurred within the 30-day safety window.
- 6.34 The submission presented an updated safety report, which provided outcomes for 10,046 patients treated with ribociclib over a reporting period of March 2021 to March 2023. In these two years, there were 2,829 cases of myelosuppression of which 1,730 were reported as serious and 37 were life-threatening or fatal. There were also 260 cases of QT interval prolongation reported of which all cases were serious, and 32 cases were life-threatening ($N = 7$) or fatal ($N = 25$), and 31 cases of fatal hepatobiliary toxicity¹¹. Considered together, there were 56 fatal events recorded, and 37 classified as "life-threatening or fatal", leading to a total of 93/10,046 (0.9%) patients with a life-threatening or fatal event, a similar proportion to the 20/2,525 (0.8%) on treatment deaths recorded in the ribociclib arm of NATALEE¹¹.

¹¹ Note that the results presented in paragraphs 6.32, 6.33 and 6.34 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.35 The discontinuation due to adverse events was higher in the ribociclib plus ET arm compared to the ET arm alone with a RD of 0.15 (95% CI: 0.13, 0.17; $p < 0.0001$)¹². In comparison, the discontinuation due to adverse events in monarchE led to a RD of 0.05 (95% CI: 0.04, 0.06; $p < 0.00001$) (Table 8)¹². The submission stated that the NATALEE trial included patients who discontinued any treatment component whereas monarchE only included those who discontinued both treatment components. The submission stated that this was likely to bias the results against ribociclib plus adjuvant ET. The submission stated that the discontinuation rate of ribociclib in NATALEE of 19.5% was similar to the discontinuation rate of abemaciclib in monarchE (18.5%)¹².

¹² Note that the results presented in paragraph 6.35 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 8: Summary of key adverse events in the trials

Trial ID / AEs	Ribociclib + ET n with event/N (%)	ET alone n with event/N (%)	RD (95% CI)
Mean duration of exposure months (SD)	32.8 (12.83)	31.9 (13.66)	
NATALEE (safety set population) July 2023 DCO (median follow-up 40.3 mths)			
Any TEAE	2474/2525 (98.0%)	2145 / 2442 (87.8%)	NR
Grade ≥ 3 TEAE	1607/2525 (63.6%)	469 / 2442 (19.2%)	
Any SAE	357/2525 (14.1%)	256 / 2442 (10.5%)	NR
Discontinuation due to AEs ^a	524/2525 (20.8)	134 / 2442 (5.5%)	NR
AEs of special interest	2183/2525 (86.5%)	1179 / 2442 (48.3%)	NR
All deaths	83/2525 (3.3%)	89 / 2442 (3.6%)	NR
On treatment deaths*	20/2525 (0.8%)	9 / 2442 (0.4%)	NR
NATALEE (safety set matching PBS subgroup) July 2023 DCO (median follow-up 40.3 mths)			
Any TEAE	1616/1644 (98.3%)	1369 / 1562(87.6%)	NR
Grade ≥ 3 TEAE	1070/1644 (65.1%)	301 / 1562 (19.3%)	NR
Any SAE	232/1644 (2.6%)	171/ 1562 (10.9%)	NR
Discontinuation due to AEs ^a	328/1644(20.0%)	74/ 1562 (4.7%)	NR
AEs of special interest	1437/1644 (87.4%)	763/ 1562 (48.8%)	NR
All deaths	68/1644 (4.1%)	72 / 1562 (4.6%)	NR
On treatment deaths	13/1644 (0.8%)	6 / 1562 (0.4%)	NR
NATALEE (safety set matching the monarchE ITT eligible) July 2023 DCO (median follow-up 40.3 mths)			
Any TEAE	1,851 / 1888 (98.0)	1,556 / 1789 (87.0)	0.11 (0.09, 0.13); p < 0.0001
Grade ≥ 3 TEAE ^b	1,206 / 1888 (63.9%)	339 / 1789 (18.9%)	0.45 (0.42, 0.48); p < 0.0001
Any SAE	270 / 1888 (14.3%)	183 / 1789 (10.2%)	0.04 (0.02, 0.06); p < 0.0001
Discontinuation due to AEs ^a	376 / 1888 (19.9%)	87 / 1789 (4.9%)	0.15 (0.13, 0.17); p < 0.0001
AEs of special interest	1,640 / 1888 (86.9%)	859 / 1789 (48.0%)	NR
All deaths	71 / 1888 (3.8%)	74 / 1789 (4.1%)	NR
On treatment deaths	20 (0.8%)	9 (0.4%)	NR
monarchE (safety population) July 2022 DCO (median follow up 42 mths)			
	Abemaciclib + ET n with event/N (%)	ET alone n with event/N (%)	RD (95% CI)
Any TEAE	2,746 / 2791 (98.4%)	2,488 / 2800 (88.9%)	0.10 (0.08, 0.11); p<0.00001
Grade ≥ 3 TEAE ^b	1,393 / 2791 (49.9%)	472 / 2800 (16.9%)	0.33 (0.31, 0.35); p<0.00001
Any SAE	433 / 2791 (15.5%)	256 / 2800 (9.1%)	0.06 (0.05, 0.08); p<0.00001
Discontinuation due to AEs ^a	180 / 2791 (6.4%)	30 / 2800 (1.1%)	0.05 (0.04, 0.06); p<0.00001
Deaths due to TEAE	15 / 2791 (0.5%)	11 / 2800 (0.4%)	(-0.00, 0.01); p = 0.43

Source: Table 2.5-15, p125, Table 2.5-16, p127 Table 2.6-9, p135 of the submission. Table 12-1e of aus_hta_t12_01e of Appendix 10. AEs = adverse events; CI = confidence interval; DCO = data cut-off; ET = endocrine therapy; mths = months; n = number of participants with event; N = total participants in group; NR= not reported; RD = risk difference; SAE = serious adverse events; TEAE = treatment-emerging adverse event; SAE = serious adverse event.

^a Discontinuation rate refers to any treatment component in NATALEE and all treatment components in monarchE.

^b Calculations conducted during the evaluation.

Bold indicated statistically significant results

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

6.36 The summary of Grade ≥ 3 TEAEs of interest is presented in Table 9. There were statistically significantly more patients treated with ribociclib plus adjuvant ET experienced Grade ≥ 3 neutropenia (RD 0.09, 95% CI: 0.07, 0.12; p < 0.0001) and ALT

increased (RD 0.04, 95% CI: 0.03, 0.05; $p < 0.0001$)¹³. Similarly, there were statistically significantly more patients treated with abemaciclib that experienced diarrhoea compared to ribociclib (RD=-0.07; 95% CI: -0.08, -0.06; $p < 0.0001$)¹³. The evaluation considered that the latter suggests that safety profiles of the two drugs are different.

- 6.37 Ribociclib was associated with a statistically higher risk of Grade 3 TEAE neutropenia and increased ALT. On the other hand, abemaciclib is associated with a higher risk of Grade 3 leukopenia, lymphopenia and diarrhoea.
- 6.38 The submission reported specific Grade 3/4 AEs in NATALEE and monarchE (Table 9), however did not present a comparison of all Grade 3/4 AEs. An anchored comparison performed during the evaluation demonstrated ribociclib was associated with statistically significantly more Grade 3/4 AEs than abemaciclib, with an odds ratio of 1.50 (95% CI 1.25, 1.79), and a significant risk difference of 0.12 (Table 8)¹³. These results suggest that for every 100 patients treated with ribociclib plus ET instead of abemaciclib plus ET, approximately 12 additional Grade 3/4 AEs may be experienced¹³. The latter suggests that the claim for non-inferior safety may not hold. However, this result was calculated by the evaluation noting that the study was not powered to detect any difference. Therefore, the evaluation considered that this result should be considered indicative only.

¹³ Note that the results presented in paragraphs 6.36 and 6.38 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 9: Summary of Grade ≥ 3 AEs (safety set)

Trial ID / AEs	Ribociclib + ET n with event/N (%)	ET alone n with event/N (%)	RD (95% CI)
NATALEE (safety set population) July 2023 DCO (median follow-up 40.3 mths)			
Neutropenia	707/2525 (28.0%)	14/2442 (0.6%)	0.27 (0.26, 0.29); p < 0.0001
Neutrophil count decreased	448/2525 (17.7%)	8/ 2442 (0.3%)	0.17 (0.16, 0.19); p < 0.0001
Alanine aminotransferase increased	192/2525 (7.6%)	17/ 2442 (0.7%)	0.07 (0.06, 0.08); p < 0.0001
Aspartate aminotransferase increased	118/2525 (4.7%)	13/ 2442 (0.5%)	0.04 (0.03, 0.05); p < 0.0001
White blood cell count decreased	94/2525 (3.7%)	6/ 2442 (0.3%)	0.03 (0.03, 0.04); p < 0.0001
Leukopenia	94/2525 (3.7%)	2/ 2442 (0.1%)	0.04 (0.03, 0.04); p < 0.0001
Diarrhoea	366 / 2525 (14.5%)	135 / 2442 (5.53%)	NR
NATALEE (safety set matching the PBS subgroup) July 2023 DCO (median follow-up 40.3 mths)			
Neutropenia	465 /1644 (28.3)	6 / 1562 (0.4%)	NR
Leukopenia	61/1644 (3.7%)	2/ 1562 (0.1%)	NR
Diarrhoea	7 / 1644 (0.4%)	2 / 1562 (0.1%)	NR
Lymphopenia	18/1644 (1.1%)	2 / 1562 (0.1%)	NR
Neutrophil count decreased	317/1644 (19.3%)	6/ 1562(0.4%)	NR
Alanine aminotransferase increased	115/1644(7.0%)	12/ 1562(0.8%)	NR
Aspartate aminotransferase increased	72/1644(4.4%)	9/ 1562(0.6%)	NR
White blood cell count decreased	76/1644(4.6%)	4/ 1562 (0.3%)	NR
Hypertension	36/1644 (2.2%)	37/ 1562 (2.4%)	NR
Arthralgia	19/1644 (1.2%)	17/ 1562 (1.1%)	NR
NATALEE (safety set matching the monarchE ITT) July 2023 DCO (median follow-up 40.3 mths)			
Neutropenia	535/1888 (28.3%)	8/1789 (0.4%)	0.28 (0.26, 0.30) p< 0.00001
Leukopenia	71/1888 (3.8%)	2/1789 (0.1%)	0.04 (0.03, 0.05) p< 0.00001
Diarrhoea	9/1,888 (0.5)	3/1,789 (0.2)	0.00 [-0.00; 0.01]; p = 0.0961
Lymphopenia	9/1,888 (0.5)	0/1,789 (0)	0.00 [0.00; 0.01]; p = 0.0044
Alanine aminotransferase increased	128/1888 (6.8%)	15/1789 (0.8%)	0.06 (0.05, 0.07) p< 0.00001
Neutrophil count decreased	343/1888 (18.2%)	7/1789 (0.4%)	NR
Aspartate aminotransferase increased	82/1888 (4.3%)	10/1789 (0.6%)	NR
White blood cell count decreased	78/1888 (4.1%)	6/1789 (0.3%)	NR
Hypertension	38/1888 (2.0%)	41/1789 (2.3%)	NR
Arthralgia	20/1888 (1.1%)	22/1789 (1.2%)	NR
monarchE (safety population) July 2022 DCO (median follow up 42 mths)			
	Abemaciclib + ET n with event/N (%)	ET alone n with event/N (%)	RD (95% CI)
Neutropenia	548/2791 (19.6%)	24/2800 (0.9%)	0.19 (0.17, 0.20) p< 0.00001
Leukopenia	318/2791 (11.4%)	11/2800 (0.4%)	0.11 (0.10, 0.12) p< 0.00001
Diarrhoea	219/2791 (7.8%)	6/2800(0.2%)	0.08 (0.07, 0.09) p< 0.00001
Lymphopenia	151/2791 (5.4%)	14/2800 (0.5%)	0.05 (0.04, 0.06) p< 0.00001

Source: Table 2.5-15, p125 and Table 2.5-17, p128 of the submission. Table 12-4e of aus_hta_t12_04e of Appendix 10.

AEs = adverse events; CI = confidence interval; DCO = data cut-off; ET = endocrine therapy; mths = months; n = number of participants with event; N = total participants in group; NR = not reported; RD = risk difference; SAE = serious adverse events; TEAE = treatment-emerging emerging adverse event; SAE = serious adverse event ^

^One person had grade 5 diarrhoea.

Bold indicated statistically significant results

Note that the results presented in Table 9 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.39 A summary of the indirect comparison for the safety results is presented in Table 10. The ITC for safety outcomes was presented for the patients in NATALEE who would have been eligible for the ITT population of monarchE (72.1% of NATALEE ITT

population) versus the safety population in monarchE (99% of ITT). The NATALEE population presented in this analysis was larger than the nominated PBS population.

6.40 At the latest DCO (July 2023), 20.7% of patients in the NATALEE trial were still receiving ribociclib, compared to all patients in monarchE having completed the treatment phase with abemaciclib.

Table 10: Bucher indirect comparison of efficacy outcomes for the nominated PBS population

TEAE	RD (95% CI); p value	RR (95% CI); p value	OR (95% CI); p value
Ribociclib + ET[^] experiencing more events			
Discontinuation due to AEs*	0.10 (0.08, 0.12); p < 0.0001	0.68 (0.44, 1.06); p = 0.0902	0.76 (0.48, 1.21); p = 0.2486
Grade 3/4 adverse events	NC	1.14 (0.99, 1.30) ^a p= 0.06	1.54 (1.27, 1.87)^a p=0.00
No difference in events between ribociclib and abemaciclib			
Any TEAE	0.01 (-0.02, 0.04); p = 0.4330	1.02 (1.00, 1.04); p = 0.1166	0.98 (0.61, 1.57); p = 0.9305
Any SAE	-0.02 (-0.05, 0.01); p = 0.1169	0.82 (0.66, 1.04); p = 0.0962	0.80 (0.62, 1.04); p = 0.0945
On-treatment deaths	0 (-0.01, 0.01); p = 1.00	1.61 (0.47, 5.52); p = 0.4461	1.62 (0.47, 5.57); p = 0.4438

Source: Table 2.6-14, p 151 of the submission.

ABE = abemaciclib; AEs = adverse even; CI = confidence interval; ITT = intent-to=treat; NC = not calculated; OR= odds ratio; RIB = ribociclib; RD= risk difference; RR= relative risk; ET = endocrine therapy; TEAE = treatment-emergent adverse event; SAE = serious adverse event.

[^] NATALEE (monarchE ITT population-eligible) Post-hoc subgroup; monarchE (Safety Set) population.

* Discontinuation rate refers to any treatment component in NATALEE and all treatment components in monarchE.

^a This result was calculated by the evaluation noting that the study was not powered to detect any difference.

NATALEE was based on the July 2023 DCO and monarchE was based on the July 2022 DCO

Bold indicates statistically significant difference.

Note that the results presented in Table 10 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.41 The results for the ITC for Grade ≥3 TEAEs of interest is presented in Table 11. There were statistically significantly more patients treated with ribociclib + adjuvant ET experienced Grade ≥ 3 neutropenia (RD 0.09, 95% CI: 0.07, 0.12; p < 0.0001) and ALT increased (RD 0.04, 95% CI: 0.03, 0.05; p < 0.0001)¹⁴. Similarly, there were statistically significantly more patients treated with abemaciclib that experienced diarrhoea compared to ribociclib (RD=-0.07; 95% CI: -0.08, -0.06; p < 0.0001)¹⁴. The evaluation considered that the latter suggests that safety profiles of the two drugs are different.

¹⁴ Note that the results presented in paragraph 6.41 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 11: Bucher indirect comparison of Grade ≥ 3 TEAEs

TEAE	RD (95% CI); p value	RR (95% CI); p value	OR (95% CI); p value
Ribociclib + ET[^] experiencing more Grade ≥ 3 TEAEs			
Neutropenia	0.09 (0.07, 0.12); p < 0.0001	2.77 (1.24, 6.19); p = 0.0132	3.12 (1.38, 7.03); p = 0.0062
Alanine aminotransferase increased	0.04 (0.03, 0.05); p < 0.0001	1.99 (0.96, 4.12); p = 0.0647	2.07 (0.99, 4.33); p = 0.0529
Abemaciclib + ET* experiencing more Grade ≥ 3 TEAEs			
Leukopenia	-0.07 (-0.08, -0.06); p < 0.0001	1.16 (0.25, 5.34); p = 0.8488	1.07 (0.23, 4.95); p = 0.9302
Diarrhoea	-0.08 (-0.09, -0.07); p < 0.0001	0.08 (0.02, 0.36); p = 0.0011	0.07 (0.02, 0.34); p = 0.0008
Lymphopenia	-0.05 (-0.06, -0.04); p < 0.0001	1.66 [0.09, 30.06]; p = 0.7303	1.59 [0.09, 28.84]; p = 0.7539

Source: Table 2.6.-15, p 154 of the submission.

ABE = abemaciclib; CI = confidence interval; DCO = data cut-off; ET = endocrine therapy; ITT = intention to treat; RIB = ribociclib; TEAEs = treatment-emergent adverse events.

[^] NATALEE (monarchE ITT population-eligible) based on post-hoc subgroup.

*Based on monarchE (Safety Set) population NATALEE was based on the July 2023 DCO (median follow up 40.3 months) and monarchE was based on the July 2022 DCO (median follow up 42 months).

Bold indicated statistically significant results.

Note that the results presented in Table 11 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Benefits/harms

6.42 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.43 The submission described ribociclib plus adjuvant ET as non-inferior in terms of effectiveness compared to abemaciclib plus adjuvant ET. The ESC considered that the ITC results support the claim of non-inferior effectiveness, noting the following points:

- The primary ITC results in the submission relied on a monarchE population (adjuvant AI subgroup) that may not reflect the PBS population for which abemaciclib is currently PBS-listed because it did not include patients treated with tamoxifen as adjuvant ET.
- The upper 95% CI in the ITC involving the PBS population of abemaciclib (includes abemaciclib patients taking tamoxifen) was 1.41, which traversed the 1.40 non-inferiority margin from the literature (Tanaka et al 2012). When the ITC was restricted to patients treated with abemaciclib plus AI (excluding tamoxifen patients), the upper 95% CI was 1.30, satisfying the 1.40 non-inferiority margin. The ESC noted that updated data from a later data cut-off provided in the PSCR indicated that the non-inferiority margin of 1.40 from the literature was not traversed for either of the ITCs.

- 6.44 While the PBAC noted the clinical issues raised in the evaluation with respect to transitivity issues between the NATALEE and monarchE trials, it agreed with the ESC that the claim of non-inferior effectiveness of ribociclib compared to abemaciclib was likely supported.
- 6.45 The submission described ribociclib plus adjuvant ET as non-inferior in terms of safety compared to abemaciclib plus adjuvant ET. The ESC considered that the safety comparison showed similarities and differences between ribociclib and abemaciclib, and noted the following points:
- Both trials show that ribociclib and abemaciclib have significantly higher rates of AE compared to the ET alone arm.
 - The CER noted a 2-fold increase in venous thrombotic and embolic events in the ribociclib plus ET compared to ET alone, 38 versus 19 participants respectively. Within these patients 18 (0.71%) patients had pulmonary emboli (three events being fatal) compared with 5 events in the ET arm.
 - There were 260 cases of QT interval prolongation reported for ribociclib plus ET, of which all cases were serious, and 32 cases were life-threatening (N = 7) or fatal (N = 25), and 31 cases of fatal hepatobiliary toxicity.
 - There was a small but marked increase in early deaths in those receiving ribociclib plus ET, and infections and pulmonary emboli were the most common causes and were similar in number to the deaths on abemaciclib in monarchE.
 - The difference in the duration of treatment phase between trials (5 years (NATALEE) versus 2 years (monarchE), may bias the ITC results against ribociclib, with NATALEE likely to report more TEAE.
- 6.46 The PSCR stated that ribociclib has a different but non-inferior safety profile to abemaciclib and this has been previously accepted by the PBAC in the advanced breast cancer setting (paragraph 7.1, abemaciclib PSD, March 2019). The PBAC considered that the safety profile of ribociclib in eBC is consistent with this previous determination and supported a conclusion of different but non-inferior safety.

Economic analysis

- 6.47 The submission presented a CMA on the basis that ribociclib and abemaciclib are non-inferior in terms of effectiveness and safety. In view of the therapeutic conclusions, a CMA was considered by the evaluation and the ESC to be appropriate. The key assumptions and components of the cost-minimisation approach are described in Table 12.

Table 12: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in the submission, effectiveness is assumed to be non-inferior
Therapeutic claim: safety	Based on evidence presented in the submission, safety is assumed to be non-inferior
Evidence base	Indirect comparison of ribociclib + adjuvant ET (NATALEE) versus abemaciclib + adjuvant ET (monarchE) using adjuvant ET alone as the common reference
Equi-effective doses	Ribociclib 366.0 mg QD on days 1 to 21 of a 28-day cycle + adjuvant ET for 114.8 weeks = Abemaciclib 121.34 mg BID + adjuvant ET for 91.0 weeks
Direct medicine costs	Cost per patient per course: Ribociclib = \$93,502.96 Abemaciclib = \$94,170.31
Other costs or cost offsets	Additional costs for medicine specific monitoring requirements including ECG (risk of QT prolongation), full blood counts, serum electrolytes and liver function tests as well as visits to oncologists due to dose reductions.

Source: Table 3.1-1 p178 and Table 3.4-7 p188 of the submission.

BID = twice a day; ECG = electrocardiogram; ET = endocrine therapy; mg = milligrams; QD = once a day

6.48 The equi-effective doses were estimated in the submission as:

- ribociclib 366.0 mg QD on days 1 to 21 of a 28 day cycle + adjuvant ET for 114.8 weeks;
- abemaciclib 121.34 mg BID + adjuvant ET for 91.0 weeks.

These doses were estimated based on the dosing regimen used in the NATALEE and monarchE trials and accounted for the corresponding dose reductions to manage drug related toxicities. The evaluation considered that this was appropriate.

6.49 The submission estimated the mean dose of ribociclib based on the ITT population of the NATALEE trial in which patients were treated with 400 mg of ribociclib per day. Dose reductions to 200 mg per day were required in 26.7% of patients primarily due to adverse events. The mean cumulative dose for the ITT population reported in NATALEE trial was 366.0 mg. The submission stated that the mean dose of ribociclib in the PBS subgroup in NATALEE was not available.

6.50 Patients in the PBS subgroup of the NATALEE trial have a more severe disease than the ITT population and are more likely to be treated longer and/or be more compliant with the treatment. The evaluation noted that unless the mean dose of treatment for this subgroup is provided, the impact of a more severe patient population on the benefit of ribociclib cannot be assessed.

6.51 The submission estimated the mean duration of treatment with ribociclib in the subgroup of patients in NATALEE who would have been eligible in monarchE (PBS population) from a post-hoc analysis of the time to treatment discontinuation (TTD) Kaplan-Meier curve. The treatment with ribociclib continued for 3 years or until disease recurrence or unacceptable toxicity. The analysis estimated a mean treatment

duration of 114.84 weeks for ribociclib¹⁵. The ESC noted the cost-minimised price of ribociclib is sensitive to the treatment duration of ribociclib.

6.52 The submission assumed a mean treatment duration of abemaciclib of 91 weeks (21 months) based on the monarchE trial. This was based on the mean treatment duration modelled for the economic evaluation of abemaciclib (paragraph 7.13, abemaciclib PSD, November 2023). However, the PBAC also considered abemaciclib use in clinical practice was likely to be less than the mean treatment duration reported in the monarchE trial due to treatment related toxicities and the likely older cohort treated through the PBS (paragraph 7.13, abemaciclib PSD, November 2023). The PBAC considered that a mean treatment duration of 18 months (78 weeks) was a more reasonable estimate. The impact on the price of ribociclib of reducing the treatment duration of abemaciclib from 91 weeks to 78 weeks has been tested in a sensitivity analysis (Table 14). Changing duration of treatment for abemaciclib from 91 weeks to 78 weeks decreases the cost-minimised price of ribociclib for the 42 pack by \$527.94 (14% reduction). The PSCR maintained that the abemaciclib treatment duration should be 21 months [91 weeks] based on the previous economic evaluation of abemaciclib. The ESC noted that the cost-minimised price of ribociclib is sensitive to the treatment duration applied to abemaciclib and considered this to be the key issue associated with the CMA. The ESC considered the equi-effective doses should be:

- ribociclib 366.0 mg QD on days 1 to 21 of a 28-day cycle + adjuvant ET for 114.84 weeks;
- abemaciclib 121.34 mg BID + adjuvant ET for 78 weeks.

6.53 The mean dose of abemaciclib was estimated based on monarchE in which the patients were treated with 150 mg twice daily with up to two dose reductions, to 100 mg twice daily and 50 mg twice daily. The submission assumed 29.5% and 13.9% of patients required one and two dose reductions due to adverse events, respectively (as reported in the Rugo et al. 2022 publication of monarchE). The impact of this difference on the mean dose of abemaciclib and price of ribociclib is negligible due to abemaciclib being priced the same for all dosage strengths.

6.54 The submission accounted for the cost offsets in specialist consultations arising due to the differences in prescribing profiles of ribociclib and abemaciclib and additional costs due to the differences in monitoring the treatment with the respective drugs. An additional specialist visit is assumed for every dose reduction to change the prescription (26.7% of patients in NATALEE). In monarchE, one specialist visit applied to 29.5% of patients (one dose reduction) and 2 specialist visits to 13.9% of patients. The cost of additional specialist visits for patients treated with ribociclib or

¹⁵ Note that the results presented in paragraph 6.51 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

abemaciclib were estimated to be \$22.56 or \$48.36 respectively. The evaluation and ESC considered that this may have been reasonable.

- 6.55 Costs related to disease monitoring were drug specific and were derived from the basic monitoring requirements as indicated in the respective PIs. The evaluation considered that these costs may be underestimated. In the case of ribociclib the increased risk of prolonged QT may lead, in some cases, to a questionable ECG reading which may require repeated ECGs and cardiologist reviews. Some of these might also require treatment cessation or treatment switching to abemaciclib which would require additional oncologist consultations; these costs were not considered in the submission’s cost-minimisation approach. The estimated monitoring costs for ribociclib and abemaciclib, that include the cost of specialist consultation, pathologies and imaging were \$915.91 and \$248.56, respectively.
- 6.56 The submission did not account for any costs associated with treatment-related AEs, justifying this by the non-inferior safety of ribociclib compared to abemaciclib. However, based on the clinical results presented, the safety profiles are different, which may result in different management of AEs. In the advanced setting the PBAC agreed ribociclib and abemaciclib had non-inferior safety noting differences between the safety profiles (paragraph 7.1, abemaciclib PSD, March 2019).
- 6.57 Table 13 presents the results of the CMA of ribociclib and abemaciclib.

Table 13: Results of the cost-minimisation approach

Component	Ribociclib	Abemaciclib
Cost of medicines		
Cost per pack (AEMP)	200 mg x 42 pack: \$3,715.64 200 mg x 21 pack: \$1,857.82	150 mg x 56 pack: \$4,087.85 100 mg x 56 pack: \$4,087.85 50 mg x 56 pack: \$4,087.85
Number of packs	200 mg x 42 pack: 29.95 200 mg x 21 pack: 27.61	150 mg x 56 pack: 24.75 100 mg x 56 pack: 25.25 50 mg x 56 pack: 19.75
Treatment duration (weeks)	114.84	91.00
Total cost of medicine ^a	\$93,502.96	\$94,170.31
Cost of monitoring ^b	\$915.91	\$248.56
Total cost per course	\$94,418.87	\$94,418.87

Source: Table 3.4-2 p185, Table 3.4-3 p186 and Table 3.4-7, p188 of the submission.

AEMP = approved ex-manufacturer price

^a Total cost of medicine per course is calculated by considering the number of packs required with each dose reduction as estimated in the submission.

^b Includes the cost of specialist consultation, pathologies and imaging.

- 6.58 The ESC noted the CMA used a treatment duration for ribociclib of 114.84 weeks, which was a smaller proportion of the maximum treatment duration of 156 weeks (3 years) for ribociclib than was used for abemaciclib:
- Ribociclib: 73.6% [114.84 weeks/156 weeks (3 years)] versus
 - Abemaciclib: 87.5% [91 weeks/104 weeks (2 years)].
- 6.59 Abemaciclib is currently PBS listed under a SPA. Given the confidential nature of these agreements, the submission used the published AEMP for all strengths of \$4,087.85.

6.60 Sensitivity analyses are presented in Table 14.

Table 14: Sensitivity analysis

Parameter	Price of Ribociclib (42 pack)	Difference from base case (42 pack)	Price of Ribociclib (21 pack)	Difference from base case (21 pack)
Base case	\$3,715.64	-	\$1,857.82	-
Duration of treatment with abemaciclib (Base case: 21 months, 91 weeks – 87.5% of maximum treatment duration of 2 years)				
18 months (78 weeks) - 75% of maximum treatment duration of 2 years	\$3,187.70	-\$527.94	\$1,593.85	-\$263.97
17.7 months (76.56 weeks) - 73.6% of maximum treatment duration of 2 years ^a	\$3,129.17	-\$590.47	\$1,564.59	-\$293.23
Duration of treatment with ribociclib (Base case 114.84 weeks – 73.6% of maximum treatment duration of 3 years)				
31.5 months (136.5 weeks) - 87.5% of maximum treatment duration of 3 years	\$3,147.27	-\$568.37	\$1,573.64	-\$284.18

^a 73.6% aligns with the proportion of the maximum treatment duration in the base case for ribociclib

Source: Constructed during the evaluation and preparation of the Minutes

Drug cost/patient/course

Table 15: Drug cost per patient for ribociclib and abemaciclib drugs

	Ribociclib			Abemaciclib		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Estimated mean dose	366 mg/day ^a	366 mg/day ^a	366 mg/day ^a	235.92 mg ^f	242.67 mg/day	242.67 mg/day
Mean duration	114.84 weeks ^b	114.84 weeks ^b	114.84 weeks ^b	102.70 weeks ^f	91 weeks	91 weeks
Cost per month ^c	\$3,528.26	\$3,528.26	\$3,648.78	\$4,656.31	\$4,484.30	\$4,594.71
Cost/patient/course	\$93,502 ^d	\$93,502 ^d	\$96,697 ^e	\$110,354 ^g	\$94,170 ^d	\$96,489 ^h

Source: constructed during the evaluation based on Section 3 and Section 4 of the submission.

CMA= cost minimisation approach; ITT= intention to treat; PBS= Pharmaceutical Benefit Scheme ^a Mean dose for ITT population.

^b Treatment duration from post hoc analysis provided with the submission truncated at 36 months.

^c Calculated considering 4.33 weeks per month ((Total cost/mean duration) * 4.33).

^d Based on CMA.

^e Cost to PBS (less copays) estimated by converting Cell F29 to '1' and Cells G29 to K 29 to '0' in '2d.Patients-DTG' sheet in financials workbook.

^f Median dose and median duration from Goetz et al. 2023.

^g Estimated by changing the Cell W12 in economic analysis workbook to 102.70 weeks and using the dose distribution from Goetz et al. 2023.

^h Cost to PBS (less copays) estimated by converting Cell F51 to '1' and Cells G51 to K51 to '0' in '2d.Patients-DTG' sheet in financials workbook.

Estimated PBS usage & financial implications

6.61 This submission was not considered by DUSC.

6.62 The submission applied an epidemiological approach to estimate the number of patients eligible for treatment with ribociclib/abemaciclib. The Sponsor chose to use an epidemiological approach as opposed to a market share approach due to insufficient data on the number of services processed for abemaciclib in eBC (PBS

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listed May 2024). The financial estimates presented in the submission were based on the published DPMQ and assumed that the once-in-a lifetime PBS restriction criterion for CDK4/6 inhibitors would continue to remain in place. The sources of data utilised are summarised in Table 16.

Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Evaluation comment
Eligible population		
Incidence of breast cancer	Assuming a linear projection applying an annual growth rate of 3.36% from the 2016 incidence of 17,354 cases Abemaciclib PSD November 2023, Table 15 p.35	Reasonable.
Proportion (%) HR+, HER2- BC	HR+/HER2- BC: 70% Abemaciclib PSD November 2023, Table 15 p.35	Reasonable.
Proportion (%) Stage I-III eBC	Stage I: 45.5% ^a Stage II: 36.7% Stage III: 12.8% Stage I-III: 95.03% National Cancer Control Indicators 2018	Reasonable.
Proportion (%) node positive and high risk of recurrence eBC	Total node positive: 24.6% High recurrence risk: 48.8% Nelson et al., 2022, Figure 1	Reasonable.
Proportion (%) treated with AI	81% 10% PBS sample data	The PSCR clarified (p4) that the 10% PBS sample data source did not distinguish patients by nodal status, and the proportion of patients treated with AI applies to all patients starting treatment in eBC. This estimate is therefore uncertain for the PBS population because it does not apply to node positive patients who are at high risk of recurrence.
Uptake rate		
Uptake of abemaciclib	2025: ██████ % 2026: ██████ % 2027: ██████ % 2028: ██████ % 2029: ██████ % 2030: ██████ % Assumption	Overestimated. A lower CDK4/6 inhibitor uptake rate would be more appropriate, noting that a maximum rate of 95% is very high.
Uptake of ribociclib in the CDK4/6 inhibitor-treated population	2025: ██████ % 2026: ██████ % 2027: ██████ % 2028: ██████ % 2029: ██████ % 2030: ██████ % Assumption.	Uncertain. The PBAC considered this to be an underestimate.

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Parameter	Value applied and source	Evaluation comment
Utilisation and cost of medicines		
Utilisation by dose	<p>Abemaciclib utilisation: 56 x 50 mg tablet: 13.9% 56 x 100 mg tablet: 29.5% 56 x 150 mg tablet: 56.6%</p> <p>Rugo et al., 2022 Figure 2</p> <p>Ribociclib utilisation: 21 x 200 mg tablet: 26.7% 42 x 200 mg tablet: 73.3%</p> <p>NATALEE Final iDFS Analysis and Safety Update Table 4-3 p. 39-40</p>	<p>Reasonable. However, the assumed utilisation across abemaciclib dose forms (150 mg vs. 100 mg vs. 50 mg) was based on trial observed dose reductions. These values slightly differ from those applied in the initial abemaciclib submission (50.1%; 37.9%; 12.0%) (para 6.58, abemaciclib, PSD, November 2023 PBAC meeting) which was based on PBS script data in the advanced setting. The PBAC considered the impact of this would be minimal.</p>
Duration of treatment	<p>Abemaciclib: 91 weeks, para 7.13 Abemaciclib PSD November 2023 PBAC meeting</p> <p>Ribociclib: 114.84 weeks NATALEE TTD post hoc analysis (PBS subgroup)</p>	<p>Overestimate. The PBAC previously considered that abemaciclib use in clinical practice was likely to be less than the mean treatment duration reported in the monarchE trial due to related toxicities and the likely older cohort treated through the PBS (para 7.13, abemaciclib PSD, November 2023 PBAC meeting) and that a mean treatment duration of 18 months was a more reasonable estimate.</p>
Cost of medicines	<p>Published DPMQ Abemaciclib 56 x 50 mg tablet: \$4,250.45 56 x 100 mg tablet: \$4,250.45 56 x 150 mg tablet: \$4,250.45</p> <p>Ribociclib (Estimated from CMA) 21 x 200 mg tablet: \$1,847.51 42 x 200 mg tablet: \$3,557.28</p>	<p>AEMP (42 pack: \$3,394.68, 24 pack: \$1,697.34) of ribociclib used to estimate published DPMQ was found to be different from that estimated in CMA (42 pack: \$3,715.84, 24 pack: \$1,857.82).</p>
Tests and investigations	<p>Abemaciclib: (Abemaciclib TGA PI) Full blood count: 7 ALT & AST: 7 Specialist visit: 1 (29.5%) 2 (13.9%)</p> <p>Ribociclib: (Ribociclib TGA PI) Electrocardiogram: 2 Full blood count: 10 Serum electrolytes: 3 Liver function tests: 7 Serum electrolytes & LFT: 3 Specialist visit: 1 (26.7%)</p>	<p>Underestimate. Some patients with prolonged QT might also require additional ECGs, cardiology reviews, oncologist consultations for treatment cessation ± monitoring, with additional oncologist review to switch over to abemaciclib, if appropriate. The PBAC noted the impact would be small given the event is relatively rare (see paragraph 6.34).</p>
Tests and investigation cost	<p>MBS Fee (Item) Abemaciclib: Full blood count: \$16.95 (65070) ALT & AST: \$11.65 (66503) Specialist visit: \$84.35 (116)</p> <p>Ribociclib: Electrocardiogram: \$249.95 (55129) Full blood count: \$16.95 (65070) Serum electrolytes: \$15.65 (66509)</p>	<p>Appropriate, although noting that it appeared that the submission used the full fee rather than the 80% MBS rebate.</p>

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Parameter	Value applied and source	Evaluation comment
	LFT: \$17.70 (66512) Serum electrolytes & LFT: \$17.70 (66512) Specialist visit: \$84.35 (116)	

Source: Table 4.1-1 p191 of the submission

ABS = Australian Bureau of Statistics; AI = Aromatase inhibitor; AIHW = Australian Institute of Health and Welfare, ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase, BC = breast cancer, DPMW = dispensed price maximum quantity, ET = endocrine therapy, HER2- = human epidermal growth factor receptor 2 negative, HR+ = hormone receptor positive, LFT = liver function test, PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Stage I patients were not included in the estimated population as the submission further estimated node positive status using data from Nelson et al 2022, which only included node positive patients.

6.63 Estimated use and financial implications of listing ribociclib are presented in Table 17.

Table 17: Estimated use and financial implications using published prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated ^a	1	1	1	1	1	1
Number of scripts dispensed ^b	2	3	3	4	4	4
Estimated financial implications of ribociclib						
Cost to PBS/RPBS less copayments ^c	\$ 5	\$ 6	\$ 7	\$ 8	\$ 8	\$ 9
Estimated financial implications for abemaciclib						
Cost to PBS/RPBS less copayments	-\$ 10	-\$ 10	-\$ 10	-\$ 10	-\$ 10	-\$ 10
Net financial implications						
Net cost to PBS/RPBS ^c	-\$ 10	-\$ 10	-\$ 10	-\$ 10	-\$ 10	-\$ 10
Net cost to MBS	\$ 11	\$ 11	\$ 11	\$ 11	\$ 11	\$ 11
Net cost to PBS/RPBS/MBS ^c	-\$ 10	-\$ 10	-\$ 10	-\$ 10	-\$ 10	-\$ 10

Source: Table 4.2-1 p 200, Table 4.2-2 p201, Table 4.2-3 p201 Table 4.3-4 p 204, Table 4.4-1 p205 and Table 4.5-3 p207 of the submission. PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme, SA = Services Australia, MBS = Medicare Benefits Schedule.

^a From Year 2, the number of treated patients includes patients who initiate abemaciclib therapy in the previous year and continue on their second year of treatment.

^b Assuming scripts per treatment: 13.04 (200 mg x 42 tabs: 73.26%, 200 mg x 21 tabs: 26.74%) estimated in the submission

^c Using revised DMPQ with AEMP estimated in the economic evaluation.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ 20,000 to < 30,000

⁵ \$20 million to < \$30 million

⁶ \$50 million to < \$60 million

⁷ \$60 million to < \$70 million

⁸ \$70 million to < \$80 million

⁹ \$80 million to < \$90 million

¹⁰ net cost saving

¹¹ \$0 to < \$10 million

6.64 The submission estimated the uptake rates of abemaciclib to estimate the use of ribociclib, as ribociclib would likely substitute some of the use of abemaciclib if listed. The submission assumed that % of the total eligible population are expected to commence treatment with abemaciclib in Year 1 (as the only CDK4/6 inhibitor currently available for this population) and that this increases each year to reach 95% in Year 6. [Within that population, the market share of ribociclib is estimated to be % over 6 years, if recommended for listing]. The evaluation and the ESC considered that

a lower CDK4/6 inhibitor uptake rate would be more appropriate, noting that a maximum rate of 95% is very high for this patient population. The PBAC previously noted the rapid uptake of abemaciclib in the Australian patient familiarisation program (paragraph 7.14, abemaciclib PSD, March 2023). The PSCR maintained that the estimate of 11% over 6 years for utilisation of CDK4/6 inhibitors in eBC is appropriate based on experience with the early access program for ribociclib in eBC. Recent clinical experience in patients with high-risk early breast cancer has suggested that approximately 20% of patients eligible for CDK4/6 inhibitors decline to commence these therapies for a number of reasons including risk of toxicities, age, frailty, residual toxicities from other treatments and the current restriction that permits one course of CDK4/6 inhibitors per lifetime. The PBAC consider that an 11% uptake rate would be appropriate considering these factors.

- 6.65 The submission assumed 100% therapy compliance. This may represent an overestimate. Previous PBAC advice suggested a compliance rate less than for hormonal therapy (84%) in case of abemaciclib (para 7.14, abemaciclib PSD, March 2023).
- 6.66 The cost savings estimated in the submission (net cost saving in Year 1, based on published prices) are primarily because the modelled treatment duration for ribociclib (114.84 weeks) is longer than for abemaciclib (91 weeks), and therefore the impact of the cost of the additional treatment duration for ribociclib only becomes more apparent in later years.

Financial Management – Risk Sharing Arrangements

- 6.67 No risk-sharing arrangement (RSA) was proposed in the submission. The ESC considered it would be appropriate for ribociclib to join the existing RSA for abemaciclib.

Quality Use of Medicines

- 6.68 The submission did not propose any activities to support the quality use of medicines. For abemaciclib, DUSC considered that there was uncertainty around the potential for harm, due to lack of longer-term data. DUSC noted that the results indicate there are substantial risks from treatment with abemaciclib for minimal benefit (Abemaciclib DUSC advice March 2022).

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule Authority Required listing of ribociclib, in combination with standard adjuvant endocrine therapy (ET), for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), lymph node positive, invasive, resected early breast cancer (eBC) at high risk of disease recurrence. The PBAC's recommendation for listing was based on, among

other matters, its assessment that the cost-effectiveness of ribociclib in eBC would be acceptable if it were cost minimised to abemaciclib. The PBAC considered the evidence presented in the submission demonstrated that ribociclib plus adjuvant ET has non-inferior efficacy compared to abemaciclib plus adjuvant ET, and a non-inferior but different safety profile.

7.2 The PBAC considered the equi-effective doses were:

- ribociclib 366.0 mg QD on days 1 to 21 of a 28-day cycle for 114.84 weeks;
- abemaciclib 121.34 mg BID for 76.56 weeks.

The rationale for the equi-effective doses recommended by the PBAC is provided in paragraph 7.12 below.

7.3 The PBAC noted that there was a moderate clinical need to have an alternative CDK4/6 inhibitor treatment for eBC on the PBS, in particular for patients unable to tolerate the currently PBS listed medicine, abemaciclib. The PBAC noted the consumer comments to this effect and acknowledged the psycho-social benefits to patients in terms of reducing the fear of recurrence, given that CDK4/6 inhibitors show a benefit in the curative setting.

7.4 The PBAC considered it was appropriate to align the PBS listing of ribociclib in eBC with abemaciclib in terms of time between initiation of adjuvant ET and ribociclib and allowing one line of therapy at any disease staging. Specifically:

- The PBAC did not support the submission's request to allow 12 months between initiation of adjuvant ET and ribociclib because: (1) in the NATALEE trial, more patients commenced therapy ≤ 6 months (49.4%) after starting ET than > 6 months (21.5%); (2) the mean time to initiate ribociclib treatment in the NATALEE trial was only 3.5 months; and (3) there is a clinical imperative to start timely therapy with a CDK4/6 inhibitor given patients have a high risk of BC recurrence. The PBAC recommended that therapy with ribociclib should begin within 6 months of starting ET, i.e., the time limit should match the current requirement for abemaciclib in eBC.
- The PBAC did not support the submission's request to omit the requirement for CDK4/6 inhibitors to be restricted to one line of therapy at any disease staging for breast cancer (i.e., if therapy has been prescribed for early disease, subsidy under locally advanced or metastatic disease is no longer available). The PBAC considered that the postMONARCH trial did not provide evidence to support removal of this condition, noting that only 1% of the metastatic BC patients had received prior adjuvant CDK4/6 inhibitor treatment and the trial did not have a suitable design to allow conclusions with respect to retreatment. The PBAC also noted that only 1.5% of patients in the NATALEE trial received a CDK4/6 inhibitor as a post-treatment anti-cancer therapy. The PBAC recommended that the requirement for restriction to one of line of therapy at any disease staging should be specified for ribociclib, aligning with the requirement for abemaciclib in eBC.

- 7.5 The PBAC considered that if eBC patients experience intolerance to a CDK4/6 inhibitor of a severity necessitating permanent treatment withdrawal, that they should be able to switch to another CDK4/6 inhibitor. The PBAC recommended that criteria be included in the ribociclib restriction to allow this. The PBAC considered that switching from ribociclib to abemaciclib should also be permitted under the same circumstances, and that this would require flow-on changes to the abemaciclib restriction in eBC.
- 7.6 The PBAC accepted the clinical place for ribociclib as an alternative to abemaciclib in eBC patients at high risk of recurrence in the adjuvant setting. The PBAC considered that abemaciclib plus adjuvant ET was the appropriate comparator given that it is a CDK4/6 inhibitor with a similar mechanism of action and mode of administration and is currently listed on the PBS for the proposed indication.
- 7.7 The PBAC noted that the pivotal trial evidence presented in the submission, which informed the indirect comparison and CMA, was based on one randomised controlled trial (RCT) of ribociclib (NATALEE) and one RCT of abemaciclib (monarchE). The PBAC noted that the hazard ratios (HRs) for the indirect comparisons, with respect to invasive disease-free survival (iDFS) and distant recurrence-free survival (DRFS), were close to 1 and found to be not statistically different¹⁶. The PBAC noted the transitivity concerns identified by the evaluation, which were mainly due to the exclusion of tamoxifen patients from the analysis because ribociclib is unable to be administered with tamoxifen as ET; however, was satisfied that overall, non-inferiority with respect to efficacy was reasonable based on the evidence presented from the NATALEE and monarchE trials. The PBAC agreed with the submission and the ESC that ribociclib has a different but non-inferior safety profile compared to abemaciclib, which may assist patients by providing an alternative treatment option to those who are unable to tolerate abemaciclib.
- 7.8 The PBAC supported the submission's approach to present a CMA on the basis that ribociclib and abemaciclib are non-inferior in terms of effectiveness and safety. The PBAC noted that the CMA in the submission accounted for the cost of the medicines (incorporating dose reductions), the cost of monitoring (incorporating consultations, pathologies and imaging), and the durations of treatment (based on the PBS subgroup of patients in the ribociclib NATALEE trial and the abemaciclib monarchE trial).
- 7.9 The PBAC considered there was some uncertainty in determining the equi-effective doses using the trial-based duration of therapies proposed by the submission, as they were based on data from different trials. In this context, the PBAC considered that for the estimation of equi-effective doses, that in line with the clinical claim of non-

¹⁶ Note that the results presented in paragraph 7.7 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

inferiority, the proportion of the maximum treatment durations for ribociclib and for abemaciclib should be equal. The PBAC noted that the submission estimated a mean duration of treatment with ribociclib of 114.84 weeks which is 73.6% of the maximum treatment duration¹⁷. The PBAC considered that it would be reasonable to assume that both ribociclib and abemaciclib would be used for 73.6% of the maximum treatment duration for each agent (114.84 weeks and 76.56 weeks, respectively).

- 7.10 The PBAC noted that because of the short time that abemaciclib has been listed on the PBS for use in eBC that a market share approach was not able to be used to estimate the utilisation of ribociclib. The PBAC considered that there were several uncertainties associated with the inputs employed in the epidemiological approach, such as treatment duration, compliance (overestimated at 100% for ribociclib; the PBAC considered that 84% was more reasonable (see paragraph 6.65)), monitoring costs (underestimated for ribociclib), uptake rate of CDK4/6 inhibitors in the eBC population (overestimated), and the market share of ribociclib within the eBC population treated with CDK4/6 inhibitors (underestimated). However, given listing is proposed based on a CMA, the PBAC considered it would be appropriate for ribociclib to join the existing RSA for abemaciclib.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ribociclib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over abemaciclib, and not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new indications as follows:

¹⁷ Note that the results presented in paragraph 7.9 are derived from post-hoc analyses conducted by the applicant during the evaluation specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the NATALEE trial. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RIBOCICLIB					
ribociclib 200 mg tablet, 21	NEW MP	1	21	5	Kisqali
ribociclib 200 mg tablet, 42	NEW MP	1	42	5	Kisqali
Restriction Summary / Treatment of Concept: [New 1]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
	Administrative Advice: Non-steroidal aromatase inhibitors for the purposes of this restriction are anastrozole and letrozole.				
	Administrative Advice: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors for the purposes of this restriction are abemaciclib, palbociclib and ribociclib.				
	Administrative Advice: The Nottingham grading system is the histologic grading system developed by Elston and Ellis as a modification of the Scarff-Bloom-Richardson grading system. See the following literature publication for details: Elston, CW, Ellis, IO. Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991 Nov;19(5):403-10.				
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.				
	Indication: Early breast cancer				
	Clinical criteria:				
	The treatment must be adjuvant to surgical resection				
	AND				
	Clinical criteria:				
	Patient must be untreated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitor therapy; OR				
	Patient must have developed an intolerance to another CDK4/6 inhibitor therapy (other than this drug) of a severity necessitating permanent treatment withdrawal				
	AND				
	Clinical criteria:				
	The condition must not have been treated with adjuvant endocrine therapy for more than 6 months prior to commencing this drug				
	AND				

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	Clinical criteria:
	The condition must be human epidermal growth factor receptor 2 (HER2) negative
	AND
	Clinical criteria:
	The condition must be hormone receptor positive
	AND
	Clinical criteria:
	The condition must be at high risk of recurrence at treatment initiation with this drug, with high risk being any of: (a) cancer cells in at least 4 positive axillary lymph nodes, (b) cancer cells in 1 to 3 positive axillary lymph nodes plus at least one of: (i) tumour size of at least 5 cm in size, (ii) grade 3 tumour histology (on the Nottingham grading system)
	AND
	Clinical criteria:
	The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) a total of 3 years of active treatment (this includes any non-PBS subsidised supply if applicable), (ii) disease recurrence/progression
	AND
	Clinical criteria:
	The treatment must not be in combination with any of the following: (i) abemaciclib, (ii) olaparib, (iii) pembrolizumab
	AND
	Treatment criteria:
	Patient must be undergoing concurrent treatment with a non-steroidal aromatase inhibitor where this drug is being prescribed as a PBS-benefit
	Prescribing Instructions: Retain all pathology imaging and investigative test results in the patient's medical records.
	Prescribing Instructions: PBS-subsidised treatment with CDK 4/6 inhibitors is restricted to one line of therapy at any disease staging for breast cancer (i.e. if therapy has been prescribed for early disease, subsidy under locally advanced or metastatic disease is no longer available).
	Caution: QT interval monitoring is required for patients treated with this drug.

8.2 The PBAC recommended flow on changes to the existing restriction for abemaciclib in eBC (PBS item codes: 14105J, 14116Y and 14134X).

The PBAC noted the following flow-on changes:

Update to the clinical criteria to facilitate treatment switching from ribociclib to abemaciclib if patients experience intolerance to ribociclib.

Clinical criteria:
<ul style="list-style-type: none"> • Patient must be untreated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitor therapy; OR • Patient must have developed an intolerance to another CDK4/6 inhibitor therapy (other than this drug) of a severity necessitating permanent treatment withdrawal.

8.3 The PBAC recommended the following flow on changes to the existing restrictions for olaparib in eBC (PBS item codes: 14181J, 14261F) and abemaciclib in eBC (PBS item codes: 14105J, 14116Y and 14134X) to add ribociclib to the list of treatments that can't be given in combination.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
olaparib 100 mg tablet, 56	14181J	2	112	5	Lynparza
olaparib 100 mg tablet, 56	14216F	2	112	6	Lynparza
olaparib 150 mg tablet, 56	14208T	2	112	5	Lynparza
olaparib 150 mg tablet, 56	14215E	2	112	6	Lynparza
	Clinical criteria:				
	The treatment must not be in combination with any of the following: (i) abemaciclib, (ii) pembrolizumab.				
	Clinical criteria:				
	The treatment must not be in combination with any of the following: (i) abemaciclib, (ii) pembrolizumab, (iii) ribociclib				

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

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
abemaciclib 100 mg tablet, 56	14105J	1	56	5	Verzenio
abemaciclib 150 mg tablet, 56	14134X	1	56	5	Verzenio
abemaciclib 50 mg tablet, 56	14116Y	1	56	5	Verzenio
	Clinical criteria:				
	The treatment must not be in combination with any of the following: (i) olaparib, (ii) pembrolizumab				
	Clinical criteria:				
	The treatment must not be in combination with any of the following: (i) olaparib, (ii) pembrolizumab, (iii) ribociclib				

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.