

6.06 PALBOCICLIB, Tablet 75 mg, Tablet 100 mg, Tablet 125 mg, Ibrance[®], Pfizer Australia Pty Ltd.

1 Purpose of submission

- 1.1 This Category 2 submission requested an extension to the current Section 85 (General Schedule), Authority Required (Telephone/Electronic) listing of palbociclib to include: the treatment of patients with locally advanced (stage IIIB/IIIC) or metastatic (stage IV) hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer who have received previous endocrine therapy, in combination with fulvestrant.
- 1.2 The proposed listing was requested on the basis of cost-minimisation versus ribociclib in combination with fulvestrant, the nominated main comparator. Abemaciclib plus fulvestrant was nominated as a near market comparator.

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

| Component | Description |
|----------------|--|
| Population | Pre-/peri- or postmenopausal patients with HR+/HER2- locally advanced inoperable or metastatic breast cancer who have: <ul style="list-style-type: none"> • Received previous endocrine therapy in the (neo)adjuvant or advanced/metastatic setting; and • Experienced disease progression; and • Developed endocrine resistance; and • Not previously been treated with a CDK4/6 inhibitor or who developed an intolerance to an alternative CDK4&6 inhibitor necessitating withdrawal; and • WHO ECOG status ≤2 |
| Intervention | Palbociclib (125 mg per day orally for 3 weeks, followed by 1 week off) + Fulvestrant (500 mg IM on days 1, 15 and 28, then 4-weekly) |
| Comparator | Main comparator: ribociclib (600 mg PO QD, 3 weeks on 1 week off) + Fulvestrant (500 mg IM on days 1, 15 and 28, then 4-weekly); Near market comparator: abemaciclib + fulvestrant |
| Outcomes | Primary outcome: Progression free survival (PFS) Secondary outcomes: Overall survival (OS), Objective Response Rate (ORR), Clinical Benefit Response (CBR), Duration of Response (DoR), Health related quality of life (HRQoL) and Safety (TEAEs). |
| Clinical claim | In patients with locally advanced inoperable or metastatic HR+/HER2-negative breast cancer, palbociclib plus fulvestrant is non-inferior in terms of efficacy and similar in terms of safety to ribociclib plus fulvestrant. |

Source: Table 1.1.1, pp6-7 of the submission.

CDK 4&6 = cyclin dependent kinase 4&6 inhibitor; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group performance status score; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; IM = intramuscular injection; PO = per oral; QD = once daily; TEAEs = treatment-emergent adverse events; WHO = World Health Organisation.

2 Background

Registration status

- 2.1 Palbociclib is TGA-registered for the treatment of HR+, HER2– advanced or metastatic breast cancer in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy or fulvestrant in patients who have received prior therapy.
- 2.2 Palbociclib 75 mg, 100 mg and 125 mg capsules were TGA registered on 3 May 2017 while palbociclib 75 mg, 100 mg and 125 mg tablets were registered on 3 June 2020. Palbociclib capsules were delisted and replaced with palbociclib tablets on 1 January 2022. The proposed listing in the current submission is for palbociclib 75 mg, 100 mg and 125 mg tablets.
- 2.3 The U.S. Food & Drug Administration granted regular approval to palbociclib in combination with fulvestrant for the treatment of HR+, HER2- advanced or metastatic breast cancer in women with disease progression following endocrine therapy in February 2016.¹ The approved indication was expanded to men in April 2019.² The European Medicines Agency granted its authorisation in November 2016.³

Previous PBAC consideration

- 2.4 The PBAC recommended the listing of palbociclib in combination with a non-steroidal aromatase inhibitor (NSAI) (anastrozole or letrozole) as initial endocrine-based therapy in patients with HR+, HER2- locally advanced inoperable or metastatic breast cancer at the March 2018 PBAC meeting (paragraph 6.1, palbociclib public summary document (PSD), March 2018).
- 2.5 The PBAC recommended the listing of ribociclib in combination with fulvestrant for the treatment of patients with HR+, HER2- unresectable advanced or metastatic breast cancer at the November 2020 meeting (paragraph 5.1, ribociclib PSD, November 2020).
- 2.6 The PBAC recommended the listing of abemaciclib in combination with fulvestrant for the treatment of non-premenopausal patients with HR+, HER2– inoperable locally advanced or metastatic breast cancer, on a cost-minimisation basis with ribociclib plus fulvestrant at the March 2021 meeting (paragraph 7.1, abemaciclib PSD, March 2021).

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

¹ U.S. Food & Drug Administration (available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/palbociclib-ibrance>; accessed 10 December 2021).

² Wedam S, Fashoyin-Aje L, et al. FDA Approval Summary: Palbociclib for Male Patients with Metastatic Breast Cancer. *Clin Cancer Res*. 2020 Mar 15;26(6):1208-1212.

³ Ibrance: European Public Assessment Report – Product Information, European Medicines Agency, first published November 2016, updated July 2021 (available at: https://www.ema.europa.eu/documents/product-information/ibrance-epar-product-information_en.pdf; accessed 10 December 2021).

3 Requested listing

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|--|-------------|---|--------------------------------------|
| PALBOCICLIB Tablets 75 mg, 100 mg, 125 mg, 21 | 21 | 5 | Published: \$4,249.07 Effective: \$1 | Ibrance® Pfizer Australia Pty Ltd |
| Category/Program: | GENERAL – General Schedule (Code GE) | | | |
| PBS indication: | Locally advanced or metastatic breast cancer | | | |
| Treatment phase: | Initial treatment | | | |
| Restriction: | Authority Required – Telephone, Electronic | | | |
| Clinical criteria: | Patient must be untreated with each of: (i) abemaciclib, (ii) palbociclib, (iii) ribociclib; or Patient must have developed an intolerance to at least one of the above drugs (other than this drug) of a severity necessitating permanent treatment withdrawal AND The condition must be hormone receptor positive AND The condition must be human epidermal growth factor receptor 2 (HER2) negative AND The condition must be inoperable AND Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less AND The treatment must be in combination, where the patient has never been treated with endocrine therapy for advanced/metastatic disease, with one of: (i) anastrozole or (ii) letrozole OR The treatment must be in combination, where the patient has recurrence/progressive disease despite being treated with endocrine therapy in the (neo)adjuvant setting or for advanced/metastatic disease, with fulvestrant only AND The treatment must not be in combination with another drug of the same pharmacological class as this drug | | | |
| Population criteria: | Patient must not be premenopausal. | | | |
| Treatment phase: | Continuing treatment | | | |
| Clinical criteria: | Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not have developed disease progression while being treated with this drug for this condition AND The treatment must be in combination with one of: (i) anastrozole, (ii) letrozole, (iii) fulvestrant AND The treatment must not be in combination with another drug of the same pharmacological class as this drug | | | |
| Population criteria: | Patient must not be premenopausal. | | | |

Source: Tables 1.4.1-1.4.3, pp21-24 of the submission

AEMP = Approved ex-manufacturer price; DPMQ = Dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme

- 3.1 The requested effective approved ex-manufacturer price (AEMP) for palbociclib (\$1), when used in combination with fulvestrant, was the same that for the current listing of palbociclib, when used in combination with an NSAID. The submission requested that the Special Pricing Arrangement (SPA) pertaining to the current palbociclib listing be applied to the extended listing. Also, the submission suggested that palbociclib's

extended listing would be included within the existing Risk Sharing Agreement (RSA) that palbociclib currently shares with ribociclib and abemaciclib.

- 3.2 The proposed restriction was largely consistent with the trial, TGA product information and clinical guidelines. The proposed PBS population includes patients who develop an intolerance to a cyclin D-dependent kinase 4/6 (CDK4/6) inhibitor of a severity necessitating permanent treatment withdrawal. However, patients who received prior treatment with any CDK4/6 inhibitors were excluded from the PALOMA-3 trial. No evidence on the clinical effectiveness and safety for patients who switched between CDK4/6 inhibitors was presented, although both the key comparator trials, MONALEESA-3 (ribociclib) and MONARCH 2 (abemaciclib), also excluded this group of patients.
- 3.3 In addition, although the submission described the proposed population as “pre-/peri or postmenopausal” patients (Table 1), this was inconsistent with the proposed wording of restriction, which stated that the “patient must not be premenopausal.” As such the requested population was more restricted than the PALOMA-3 palbociclib trial population, in which 20.3% of patients were pre/perimenopausal. This is appropriate as fulvestrant is TGA-indicated for the treatment of postmenopausal women only. The current PBS-listings for ribociclib and abemaciclib also require patients to not be premenopausal.
- 3.4 The proposed PBS population for palbociclib plus fulvestrant was "narrower" than the current PBS-listed populations for ribociclib plus fulvestrant and abemaciclib plus fulvestrant. Ribociclib or abemaciclib plus fulvestrant may be used in patients who have not been treated with endocrine therapy for advanced/metastatic disease; whereas, the proposed restriction for palbociclib plus fulvestrant does not allow use in these patients. Palbociclib plus fulvestrant, unlike ribociclib or abemaciclib plus fulvestrant, is not TGA-approved as initial endocrine-based therapy.
- The MONARCH 2 trial (abemaciclib plus fulvestrant) included only limited evidence for the de novo locally advanced/metastatic disease subgroup. Only a post hoc exploratory analysis of 44 patients was available to inform the clinical effectiveness and safety of abemaciclib in this group (paragraph 3.2, abemaciclib PSD, March 2021).
 - The PBAC has previously noted the use of CDK inhibitors plus fulvestrant is “likely to be minimal in de novo patients as these patients would likely prefer an oral NSAI than intramuscular injections of fulvestrant” and therefore, the PBAC considered that “a listing, including de novo metastatic patients, would be appropriate for abemaciclib and consistent with both the TGA registered indication for abemaciclib and the listing recommended for ribociclib at the November 2020 PBAC meeting” (paragraph 7.3, abemaciclib PSD, March 2021).
- 3.5 The submission requested a grandfathering provision for palbociclib’s extended listing in combination with fulvestrant.

- The submission anticipated that < 500 patients enrolled in a compassionate access program would require grandfathering onto PBS-reimbursed palbociclib treatment. The submission included these < 500 patients in the estimated number of treated patients in Year 1 of listing in its financial estimates.
- The proposed wording of restriction for patients transitioning from non-PBS to PBS-subsidised supply was broadly similar to the current wording for grandfather arrangements with abemaciclib (listed since 1 November 2021).

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

4 Population and disease

- 4.1 Breast cancer is estimated to be the most commonly diagnosed cancer and second most common cause of death from cancer in females in 2021.⁴ Despite improvement in overall survival with systemic therapies, metastatic breast cancer is still considered incurable, with a median survival of approximately 18-24 months after diagnosis.⁵ The goals of treatment are to improve survival, and improve or maintain quality of life.
- 4.2 The target population are patients with HR+ and HER2- locally advanced or metastatic breast cancer who have received previous endocrine therapy. This includes patients who have “recently become resistant to (i.e. experienced disease progression) endocrine therapy either whilst on, or within 12 months of completing, (neo)adjuvant treatment. It also includes patients already with advanced disease that have become resistant to endocrine therapy in the advanced setting.” The clinical algorithm presented in the submission reflected Australian clinical practice and was broadly similar to the algorithm seen by the PBAC during its consideration of abemaciclib in March 2021 (Figure 1, p8, Abemaciclib PSD, March 2021 PBAC Meeting).
- 4.3 Palbociclib is a cyclin D-dependent kinases (CDK) 4 and 6 inhibitor.
- 4.4 If approved, palbociclib would be the third CDK4/6 inhibitor available on the PBS for the target population.

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

5 Comparator

- 5.1 The submission nominated ribociclib plus fulvestrant as the main comparator because ribociclib is a close pharmacological analogue to palbociclib and because ribociclib plus fulvestrant is the treatment likely to be substituted the most by the proposed listing of palbociclib plus fulvestrant. The ESC considered that this was appropriate.

⁴ Australian Institute of Health and Welfare 2021. *Cancer in Australia 2021*. Cancer series no. 133. Cat. no. CAN 144. Canberra: AIHW.

⁵ Therapeutic Goods Administration, Clinical Evaluation Report - Prescription Medicines Authorisation Branch – Palbociclib, second round report, p15.

- 5.2 The PBAC has previously accepted ribociclib in combination with fulvestrant as the main comparator for abemaciclib in combination with fulvestrant at its March 2021 meeting, noting that ribociclib is a close pharmacological analogue to abemaciclib. The current submission has a similar target population to that proposed for abemaciclib in combination with fulvestrant (para. 5.1, Abemaciclib PSD, March 2021 PBAC Meeting). The ESC noted that this further supported ribociclib plus fulvestrant for the main comparator in the current assessment.
- 5.3 Abemaciclib plus fulvestrant was nominated as a near market comparator as abemaciclib is a listed pharmacological analogue to palbociclib for the same requested indication. The ESC noted that abemaciclib plus fulvestrant was listed on the PBS on 1 November 2021 and could be considered a secondary comparator.
- 5.4 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. Ribociclib and abemaciclib are alternate therapies to palbociclib.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The Medical Oncology Group of Australia (MOGA) expressed its support for palbociclib for use in combination with fulvestrant. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for palbociclib, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)⁶, based on a comparison with fulvestrant in the PALOMA-3 trial.

Clinical trials

- 6.3 No direct randomised trials were available to inform the comparison of palbociclib plus fulvestrant versus ribociclib plus fulvestrant or abemaciclib plus fulvestrant.

⁶ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Instead, the comparative clinical effectiveness and safety data were based on anchored indirect comparisons.

- 6.4 The submission was based on the following trial of palbociclib:
- PALOMA-3 (N=521): a randomised controlled trial (RCT) comparing palbociclib plus fulvestrant to placebo plus fulvestrant in women (any menopausal status) with HR+, HER2- advanced breast cancer whose disease relapsed or progressed during/after prior endocrine therapy (expected completion in May 2022).
- 6.5 The submission also presented the following trials involving other CDK4/6 inhibitors:
- MONALEESA-3 (N=726): a RCT comparing ribociclib plus fulvestrant to placebo plus fulvestrant in postmenopausal women with HR+/HER2- advanced breast cancer (expected completion in September 2022). The PBAC previously considered the MONALEESA-3 trial during its evaluation of ribociclib at its July 2020 Meeting and abemaciclib at its March 2021 Meeting. The PBAC has not seen the most recent exploratory survival data for the MONALEESA-3 trial (longer follow-up of median 56.3 months, see **Error! Reference source not found.** and **Error! Reference source not found.**).
 - MONARCH 2 (N=669): a RCT comparing abemaciclib plus fulvestrant to placebo plus fulvestrant in patients with premenopausal or perimenopausal women (with ovarian suppression) and postmenopausal women with HR+, HER2- advanced breast cancer that progressed during endocrine therapy (expected completion in January 2024). The PBAC previously evaluated the MONARCH 2 trial during its consideration of abemaciclib at its March 2021 Meeting.
- 6.6 The submission presented two indirect comparisons (Bucher method) using placebo plus fulvestrant as the common comparator:
- Palbociclib vs. ribociclib: PALOMA-3 and MONALEESA-3; and
 - Palbociclib vs. abemaciclib: PALOMA-3 and MONARCH 2.
- 6.7 Details of the key trials are provided in **Table 22**.

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Table 2: Trials and associated reports presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|--|---|
| PALOMA-3 (Study A5481023; NCT01942135) | Protocol & Statistical Analysis Plan (SAP) | 10 Jan 2018 |
| | 1. Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Of Fulvestrant (Faslodex) With Or Without PD-0332991 (palbociclib) ± Goserelin In Women With Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy. | <i>Clinical Study Report</i> , 5 Dec 2014 |
| | 2. Palbociclib (Pd-0332991; CDK 4/6 Inhibitor) HR-Positive, HER2-Negative Advanced Breast Cancer A5481023 (Paloma-3) Progression-Free Survival Update. | <i>Clinical Study Report</i> , 16 March 2015 |
| | 3. A5481023 – Updated Progression-Free Survival Report (data only). | 23 Oct 2015 |
| | 4. A5481023 Progression Free Survival (PFS) Update Tables only | |
| | 5. Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Of Fulvestrant (Faslodex) With Or Without PD-0332991 (palbociclib) ± Goserelin In Women With Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy. | <i>Clinical Study Report</i> , 13 April 2018 |
| | Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer | <i>NEJM</i> 2015; 373(3):209-219. |
| | Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. | <i>Lancet Oncology</i> 2016; 17(4):425-439. |
| | Harbeck N, Iyer S, Turner N, et al. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial. | <i>Ann Oncol.</i> 2016; 27(6):1047-1054. |
| | Verma S, Bartlett CH, Schnell P, et al. Palbociclib in Combination With Fulvestrant in Women With Hormone Receptor-Positive/HER2-Negative Advanced Metastatic Breast Cancer: detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase III Study (PALOMA-3). | <i>Oncologist</i> 2016; 21(10):1165-1175. |
| | Iwata H, Im SA, Masuda N, et al. PALOMA-3: phase III trial of fulvestrant with or without palbociclib in premenopausal and postmenopausal women with hormone receptor positive, human epidermal growth factor receptor 2-negative metastatic breast cancer that progressed on prior endocrine therapy safety and efficacy in Asian patients. | <i>Journal of Global Oncology</i> 2017; 3(4):289-303. |
| | Loibl S, Turner NC, Ro J, et al. Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy PALOMA-3 Results. | <i>Oncologist</i> 2017; 22(9):1028-1038. |
| Cristofanilli M, DeMichele A, Giorgetti C, et al. Predictors of prolonged benefit from palbociclib plus fulvestrant in women with endocrine-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer in PALOMA-3. | <i>European Journal of Cancer</i> 2018; 104:21-31. | |
| Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. | <i>NEJM</i> 2018; 379(20):1926-1936. | |

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| Trial ID | Protocol title/ Publication title | Publication citation |
|--------------------------------------|---|---|
| | <p>Masuda N, Inoue K, Nakamura R, et al. Palbociclib in combination with fulvestrant in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: PALOMA-3 subgroup analysis of Japanese patients.</p> <p>Rugo HS, Cristofanilli M, Loibl S, et al. Prognostic Factors for Overall Survival in Patients with Hormone Receptor-Positive Advanced Breast Cancer: Analyses From PALOMA-3.</p> <p>Kim JH, Im SA, Sim SH, et al. Palbociclib plus fulvestrant in Korean patients from paloma-3 with hormone receptor-positive/human epidermal growth factor receptor 2 negative advanced breast cancer.</p> | <p><i>International Journal of Clinical Oncology</i> 2019; 24(3):262-273.</p> <p><i>Annals of Oncology</i> 2021; 26(8):e1339-e1346.</p> <p><i>Journal of Breast Cancer</i>. 2021; 24(1):97-105.</p> |
| <p>MONALEESA-3 NCT02422615</p> | <p>Study of Efficacy and Safety of LEE011 in Men and Postmenopausal Women with Advanced Breast Cancer</p> <p>Slamon DJ, Neven P, Chai S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3.</p> <p>Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer.</p> <p>Fasching PA, Beck JT, Chan A, et al. Ribociclib plus fulvestrant for advanced breast cancer: health-related quality-of-life analyses from the MONALEESA-3 study.</p> <p>Slamon DJ, Neven P, Chia S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase 3 randomized MONALEESA-3 trial: updated overall survival.</p> | <p>Clinical Study</p> <p><i>Journal of Clinical Oncology</i>. 2018; 36(24):2465-2472.</p> <p><i>NEJM</i> 2020; 382(6):514-524</p> <p><i>Breast</i> 2020; 54:148-154</p> <p><i>Annals of Oncology</i> 2021; 32(8):1015-1024.</p> |
| <p>MONARCH – 2 (NCT02107703)</p> | <p>A Study of Abemaciclib (LY2835219) Combined with Fulvestrant in Women with Hormone Receptor Positive HER2 Negative Breast Cancer</p> <p>Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in Combination with Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy.</p> <p>Sledge GW Jr, Toi M, Neven P, et al. The Effect of Abemaciclib plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy – MONARCH 2: a Randomized Clinical Trial.</p> <p>Kaufman PA, Toi M, Neven P, et al. Health-Related Quality of Life in MONARCH 2: abemaciclib plus Fulvestrant in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer After Endocrine Therapy.</p> <p>Inoue K, Masuda N, Iwata H, et al. Japanese subpopulation analysis of MONARCH 2: phase 3 study of abemaciclib plus fulvestrant for treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer that progressed on endocrine therapy.</p> <p>Neven P, Johnston SRD, Toi M, et al. MONARCH 2: subgroup analysis of patients receiving abemaciclib plus fulvestrant as first-line and second-line therapy for HR+, HER2- advanced breast cancer.</p> | <p>Clinical Study</p> <p><i>Journal of Clinical Oncology</i> 2017; 35(25):2875-2884.</p> <p><i>JAMA oncology</i> 2020;6(1):116-124</p> <p><i>Oncologist</i> 2020;25(2):e243-e251.</p> <p><i>Breast Cancer (Tokyo, Japan)</i> 2021; 28(5):1038-1050.</p> <p><i>Clinical Cancer Research</i>. 2021; 27(21):5801-5809.</p> |

Source: Adapted from Table 2.2.2, pp36-38 of the submission.

6.8 The key features of the randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

| Trial | N | Design | Risk of bias | Patient population | Outcomes |
|--|-----|-----------------|------------------|--|--|
| Palbociclib + fulvestrant vs. Placebo + fulvestrant | | | | | |
| PALOMA-3 | 521 | R (2:1), DB, MC | Low | Pre-/peri- or postmenopausal women, HR+/HER2- aBC, not amenable to curative treatment; progressed after prior ET | Primary: PFS Key secondary: OS, QoL, safety |
| Ribociclib + fulvestrant vs. Placebo + fulvestrant | | | | | |
| MONALEESA-3 ^a | 726 | R (2:1), DB, MC | Low ^b | Postmenopausal women, HR+/HER2- aBC not amenable to curative treatment; newly diagnosed or relapse, received no or only one prior ET for aBC | Primary: PFS Key secondary: OS, safety. |
| Abemaciclib + fulvestrant vs. Placebo + fulvestrant | | | | | |
| MONARCH 2 ^a | 669 | R (2:1), DB, MC | Low ^c | HR+/HER2- women, any menopausal status, progressed while receiving (neo)adjuvant ET, ≤12 months from the end of adjuvant ET, or while receiving first-line ET for metastatic disease | Primary: PFS Key secondary: OS, QoL and safety. |

Source: Table constructed during the evaluation using information provided in Turner 2015, Slamon 2020 and Sledge 2020. aBC = advanced breast cancer; DB = double blind; ET = endocrine therapy; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; MC = multi-centre; N/A = not applicable; OS = overall survival; PFS = progression-free survival; QoL = quality of life; R (2:1) = random allocation in 2:1 ratio to receive experimental treatment or control treatment.

^a Trials were seen by the PBAC. The PBAC had previously evaluated (a) the MONALEESA-3 trial during its consideration of ribociclib at its July 2020 meeting and abemaciclib at its March 2021 meeting; and (b) the MONARCH 2 trial during its consideration of abemaciclib at its March 2021 meeting.

^b Risk of bias was low until protocol amendment, which unblinded treatment allocation and allowed cross-over of placebo control arm patients to the experimental arm.

^c A key protocol amendment involving reduction of starting dose from abemaciclib 200 mg twice daily to 150 mg twice daily to improve tolerability (121/441 patients already enrolled) might contribute to potential bias in results.

6.9 The dosing and duration of palbociclib, ribociclib, abemaciclib and fulvestrant matched the respective TGA Product Information leaflets, noting that the use of fulvestrant in pre/perimenopausal women in the PALOMA-3 (21%) and MONARCH 2 (18%) trials was outside the TGA-approved indication for fulvestrant.

6.10 There were several differences in the key eligibility criteria across the trials:

- Although all three trials included patients who were treatment-naïve for advanced disease, both the PALOMA-3 and the MONARCH 2 trials required these patients to have either relapsed while on adjuvant endocrine therapy (ET) or progressed within 12 months of completion of adjuvant ET. By contrast, the MONALEESA-3 trial required patients to have relapsed or progressed after completion rather than during adjuvant ET.
- Only the MONALEESA-3 trial included patients newly diagnosed with metastatic breast cancer who were treatment-naïve for advanced disease. The MONARCH 2 trial initially included 44 ET-naïve patients, but later excluded them from the primary analysis after a protocol amendment

- All trials included patients who relapsed while on ET for advanced disease. The PALOMA-3 trial included patients who progressed within a month of completion of ET for advanced disease. Conversely, the MONALEESA-3 and the MONARCH 2 trials included patients who relapsed more than 12 months from the completion of adjuvant ET and subsequently progressed after one line of ET for metastatic disease.
- Prior chemotherapy for advanced disease was allowed in the PALOMA-3 trial (one line only) but not in the other two trials. One-third (33%) of the patients in the PALOMA-3 trial had prior chemotherapy for advanced/metastatic disease. The National Institute for Health and Care Excellence (NICE) concluded that the results from PALOMA-3 were relevant, although it noted that the proportion of patients who had previously had chemotherapy for advanced disease was higher than expected in current NHS clinical practice.⁷
- All three trials excluded patients with prior treatment with CDK inhibitors or fulvestrant. The PALOMA-3 and MONARCH 2 trials also excluded patients with prior everolimus.

6.11 Additional factors that may affect the comparability of the treatment effect across the three trials include differing proportions of patients taking subsequent therapies and differing durations of follow-up (e.g. median 15 months of follow-up for PFS outcomes in the PALOMA-3 trial but median 39.4 and 47.7 months for the MONALEESA-3 and MONARCH 2 trials).

Comparative effectiveness

6.12 Table 44 presents a summary of the survival outcomes in the PALOMA-3 trial.

⁷ NICE 2020. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. Technology appraisal guidance [TA619]. NICE 15 January 2020.

Table 4: Survival outcomes in the PALOMA-3 trial (ITT population)

| Outcome | PAL + FUL n/N (%) | PBO + FUL n/N (%) | Absolute difference | HR (95% CI); p-value |
|--|----------------------|----------------------|------------------------|--|
| Final PFS (investigator-assessed) (data cut-off 23 Oct 2015), median FU 15.8 vs. 15.3 months (source: Palbociclib CSR) | | | | |
| Progression/death | 200/347 (57.6) | 133/174 (76.4) | -18.8% | - |
| Median PFS (95% CI), ^a months | 11.2 (9.5, 12.9) | 4.6 (3.5, 5.6) | 6.6 | 0.50 (0.40, 0.62)^b; p<0.0000 ^b |
| Final OS (data cut-off 13 April 2018, median FU 44.8 months, 60% data maturity^d) (CSR, 19 September 2018 or Turner 2018) | | | | |
| Deaths | 201/347 (57.9) | 109/174 (62.6) | -4.7% | |
| Median OS (95% CI), ^a months | 34.9 (28.8, 40.0) | 28.0 (23.6, 34.6) | 6.9 | 0.81 (0.64, 1.03) ^b ; p=0.0429 ^c |
| 3-year OS, % (95% CI) | 50 (44, 55) | 41 (33, 48) | | |
| Ad hoc exploratory (unplanned, unpublished) (data cut-off 17 August 2020, median FU 73.3 months, 75% data maturity^e) (Cristofanilli 2021 abstract) | | | | |
| Ad hoc OS | NR | NR | | |
| Median OS (95% CI), ^a months | 34.8 (28.8, 39.9) | 28.0 (23.5, 33.8) | 6.8 | 0.81 (0.65, 0.99); 1-sided nominal p=0.0221 |
| 5-year OS, % (95% CI) | 23.3 (18.7, 28.2) | 16.8 (11.2, 23.3) | | |

Source: Tables 1023.511.12 and 1023.560.1, pp58-59 in in Palbociclib (A5481023) Final PFS tables (data cut-off 23 October 2015);. Table 15, p58 in Palbociclib (A5481023) CSR Main Body Abbreviated (data cut-off 13 April 2018), 19 September 2018; 'A5481026 – Updated OS TLS_Jan 2021' included as part of large files with the submission; Cristofanilli 2021 abstract

CI = confidence interval; CSR = Clinical Study Report; FU = follow-up; FUL = fulvestrant; HR = hazard ratio; ITT = intention-to-treat; n = number of participants with event; N = total participants in group; NR = not reported; OS = overall survival; PAL = palbociclib; PBO = placebo; PFS = progression-free survival

^a 50% quartile of Kaplan-Meier estimates of time to event (based on the Brookmeyer and Crowley Method).

^b Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favour of palbociclib plus fulvestrant.

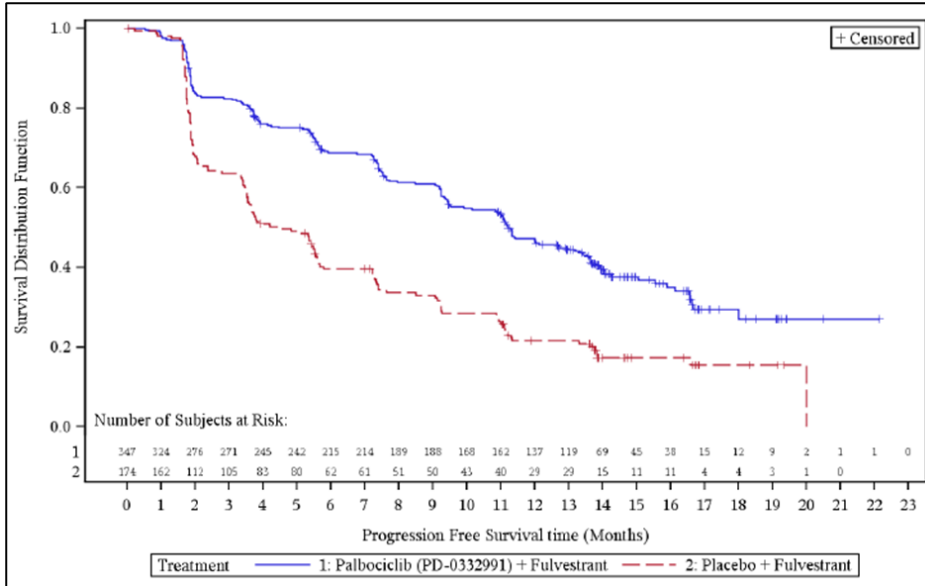
^c 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomisation.

Bold indicates statistically significant results.

- 6.13 In PALOMA-3, the investigator-assessed median PFS was 11.2 months in the palbociclib plus fulvestrant treatment group (median 15.8 months follow-up), compared with 4.6 months in the placebo plus fulvestrant group (median 15.3 months follow-up). The 6.6 month improvement in median PFS was statistically significant (HR = 0.50; 95% CI: 0.40, 0.62).
- 6.14 At a median follow-up of 44.8 months, 57.9% of the patients in the palbociclib plus fulvestrant group had died versus 62.6% in the placebo plus fulvestrant group. The submission reported that the addition of palbociclib to fulvestrant improved the secondary outcome of OS with a HR of 0.81 (95% CI: 0.64, 1.03), although the result was not statistically significant at the pre-specified significance level of 0.0235. The submission considered that the 6.9-month improvement in median OS in the palbociclib plus fulvestrant arm (34.9 months) compared with the placebo plus fulvestrant arm (28.0 months) was clinically meaningful.
- 6.15 An unplanned, updated OS analysis at a median follow-up of 73 months reported similar results.

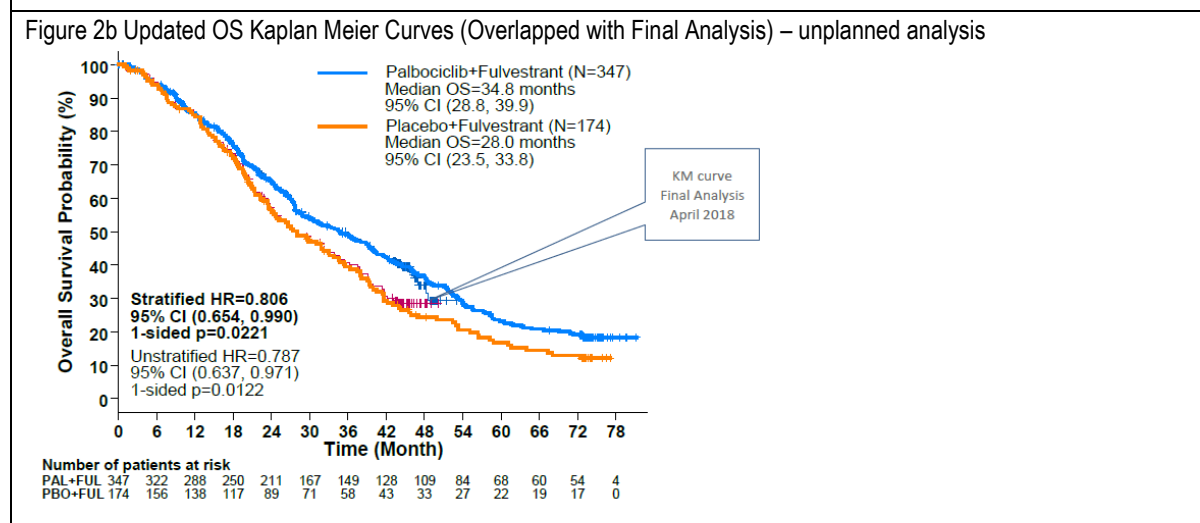
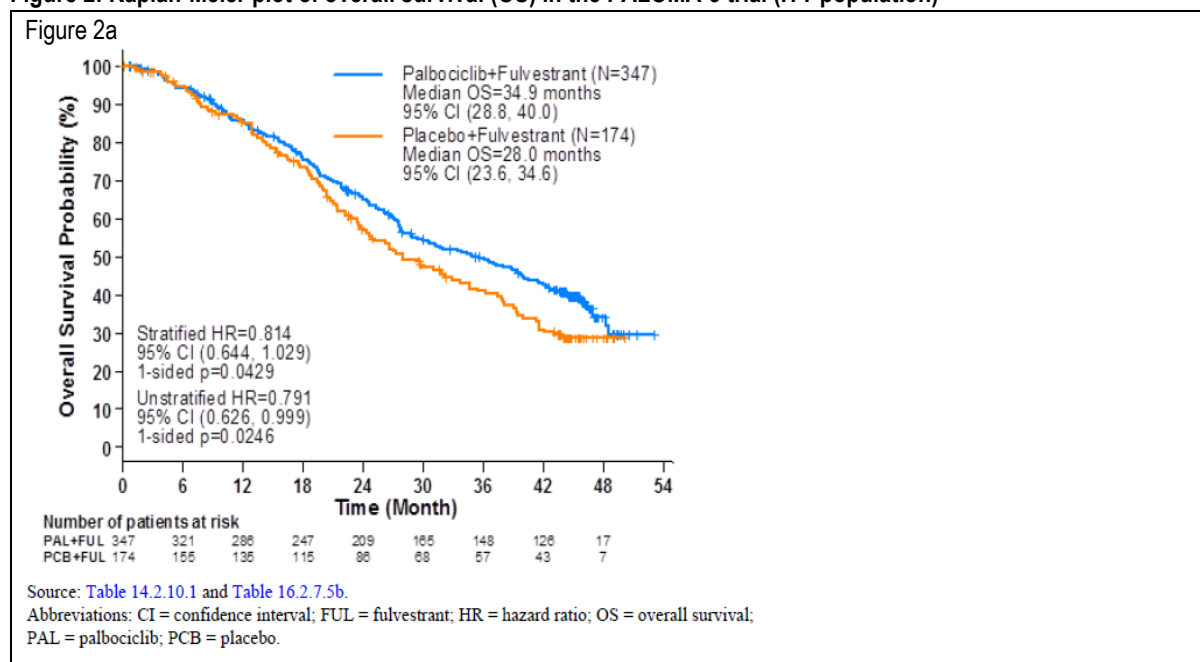
6.16 Figure 1 and Figure 2 present the Kaplan-Meier plots of PFS and OS for the ITT population respectively.

Figure 1: PALOMA-3 – PFS (investigator-assessed) (ITT population)



Source: Figure 1023.560.12, p70 of the Palbociclib (A5481023) Final PSF report (data cut-off 23 October 2015)
 ITT = intention to treat; PFS = progression-free survival

Figure 2: Kaplan-Meier plot of overall survival (OS) in the PALOMA-3 trial (ITT population)



Source: Figure 1, p59 in Palbociclib (A5481023) CSR Main Body Abbreviated (data cut-off 13 April 2018), 19 September 2018; Figure 1 in 'A5481023 – Updated OS TLS Jan 2021' included as part of large files with the submission.

CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival

Final analysis for OS was performed in 2018 with 310 events (60% of 521 total randomised patients) based on April 13, 2018 data cut-off. An updated OS analysis (unplanned) was performed in Q4 2020 with 393 events (75% of 521 total randomised patients) based on August 17, 2020 data cut-off in order to support country level health technology assessment negotiations and provided more mature results as the study team prepared for final study closure.

6.17

6.18 Table 5 and

6.19 Table 66 present the indirect comparisons of PFS (investigator-assessed) and OS, respectively from the PALOMA-3, MONALEESA-3 and MONARCH 2 trials.

- The PBAC has seen the survival outcomes (PFS, OS) from the MONALEESA-3 and the MONARCH 2 trials during the previous considerations of ribociclib (July 2020) and abemaciclib (March 2021).
- The PBAC has not previously considered data from the more recently published survival follow-up (median 56.3 months) for the MONALEESA-3 trial. PFS2, a prespecified exploratory endpoint, was defined as the time from randomisation to the first documented disease progression following discontinuation from study treatment while the patient was receiving next-line therapy (as reported by the investigator) or death from any cause, whichever occurred first.
- The MONALEESA-3 trial included treatment-naïve patients (50%) and patients with de novo metastatic disease (19%) with inherently better prognosis and treatment-responsiveness. In contrast, the PALOMA-3 trial only included endocrine-resistant patients. Therefore, the submission presented additional indirect comparison analyses using the prespecified subgroup of patients with endocrine-resistant disease in the MONALEESA-3 trial versus the PALOMA-3 trial (intention-to-treat (ITT) population). This was appropriate. A similar indirect comparison of abemaciclib versus ribociclib using the endocrine-resistant subgroup in the MONALEESA-3 trial versus the MONARCH 2 (ITT population) was evaluated by the PBAC at the March 2021 meeting (paragraph 6.17, abemaciclib PSD, March 2021).

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Table 5: Results of the indirect comparison in the submission – PFS

| | Trial Median follow up | Comparison | PFS n/N (%) | | Median PFS (95% CI), months | | HR (95% CI), p-value |
|---------|--|----------------------------|-------------------|-------------------|----------------------------------|--------------------------------|---|
| | | | Test | Control | Test | Control | |
| A | PALOMA-3 (ITT), 15.8 months | PAL + FUL vs. PBO + FUL | 200/347 (57.6) | 133/174 (76.4) | 11.2 (9.5, 12.9) ^a | 4.6 (3.5, 5.6) ^a | 0.50 (0.40, 0.62) ^b , p<0.0000 ^c |
| B | MONALEESA-3 (ITT), 39.4 months | RIB + FUL vs. PBO + FUL | 283/484 (58.5) | 193/242 (79.8) | 20.6 | 12.8 | 0.59 (0.49, 0.71)^d , p<0.0001 |
| C | MONALEESA-3 (ER ^e) 39.4 months | | 167/237 (70.5) | 95/109 (87.2) | 14.6 | 9.1 | 0.57 (0.44, 0.74)^d , p<0.0000 |
| D | MONALEESA-3 (ITT), PFS2 ^f 56.3 months | | 265/484 (54.8) | 163/242 (67.4) | 37.4 (31.1, 42.6) | 28.1 (24.0, 31.6) | 0.71 (0.57, 0.84), p=0.001 |
| E | MONALEESA-3 (ER ^e) PFS ^f 56.3 months | | 153/237 (64.6) | 80/110 (73.4) | 26.0 | 20.5 | 0.73 (0.56, 0.96), p=0.02 |
| F | MONARCH 2 (ITT) 47.7 months | ABE + FUL vs. PBO + FUL | 297/446 (66.6) | 193/223 (86.5) | 16.9 | 9.3 | 0.54 (0.45, 0.65)^d , p<0.001 |
| A vs. B | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, mFU 15.8 months) vs. MONALEESA-3 (ITT population, mFU 39.4 months) | | | | | | 0.84 (0.63, 1.13), p=0.2447 |
| A vs. C | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, mFU 15.8 months) vs. MONALEESA-3 (ER ^e , 39.4 months follow up) | | | | | | 0.87 (0.62, 1.23), p=0.4317 |
| A vs. F | Indirect comparison PAL+FUL vs. ABE+FUL: PALOMA-3 (ITT population, mFU 15.8 months) vs. MONARCH 2 (ITT population, mFU 47.7 months) | | | | | | 0.93 (0.69, 1.24), p=0.6085 |

Source: table constructed during the evaluation using information from Spreadsheets 'PFS & OS HR PAL_v_RIB' and 'PFS & OS HR PAL_v_ABE' in Excel workbook titled 'Attachment 4 Section 2 Indirect Treatment Comparisons', included as Attachment 4 of the submission; Tables 1023.511.12 and 1023.560.1, pp58-59 in in Palbociclib (A5481023) Final PSF tables (data cut-off 23 October 2015); Figures 3A and 3C in Slamon 2020; Sledge 2017; eFigure 2 in Supplement 2 of Sledge 2020; Table 6, Abemaciclib PSD, March 2021 PBAC Meeting. ABE = abemaciclib; CI = confidence interval; ER = endocrine-resistant subgroup; FUL = fulvestrant; HR = hazard ratio; ITT = intention-to-treat; mFU = median follow-up; n = number of participants with event; N = total participants in group; PAL = palbociclib; PBO = placebo; PFS = progression-free survival; RIB = ribociclib

^a 50% quartile of Kaplan-Meier estimates of time to event (based on the Brookmeyer and Crowley Method).

^b Hazard ratio less than 1 is in favour of palbociclib plus fulvestrant.

^c 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomisation.

^d Data were previously seen by the PBAC (MONALEESA-3: July 2020, November 2020 and March 2021 PBAC Meetings; MONARCH 2: March 2021 PBAC Meeting).

^e Patients who received trial treatment as second-line therapy or who had early relapse (within 12 months after completion of adjuvant or neoadjuvant endocrine therapy).

^f PFS2, a prespecified exploratory endpoint, was defined as the time from randomisation to the first documented disease progression following discontinuation from study treatment while the patient was receiving next-line therapy (as reported by the investigator) or death from any cause, whichever occurred first (Slamon 2021).

Bold indicates statistically significant results from pre-planned analyses

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Table 6: Results of the indirect comparison in the submission – OS

| | Trial Median follow up | Comparison | OS n/N (%) | | Median OS (95% CI), months | | HR (95% CI), p-value |
|---------|---|----------------------------|-------------------|-------------------|-----------------------------------|-----------------------------------|---|
| | | | Test | Control | Test | Control | |
| A | PALOMA-3 (ITT), 44.8 months | PAL + FUL vs. PBO + FUL | 201/347 (57.9) | 109/174 (62.6) | 34.9 (28.8, 40.0) ^a | 28.0 (23.6, 34.6) ^a | 0.81 (0.64, 1.03) ^b , p=0.0429 ^c |
| B | PALOMA-3 (ITT), 73.3 months ^d | | NR | NR | 34.8 (28.8, 39.9) | 28.0 (23.5, 33.8) | 0.81 (0.65, 0.99) ^b , p=0.0221 ^c |
| C | MONALEESA-3 (ITT), Final OS 39.4 months | RIB + FUL vs. PBO + FUL | 167/484 (34.5) | 108/242 (44.6) | NE (42.5, NE) | 40.0 (37.0, NE) | 0.72 (0.57, 0.92)^e , p=0.0086 |
| D | MONALEESA-3 (ER ^f), Final OS 39.4 months | | 102/237 (43.0) | 60/109 (55.0) | 40.2 | 32.5 | 0.73 (0.53, 1.00) ^e , p=NR |
| E | MONALEESA-3 (ITT), Exploratory OS 56.3 months | | 222/484 (45.9) | 142/242 (58.7) | 53.7 (46.9, NE) | 41.5 (37.4, 49.0) | 0.73 (0.59, 0.90) , p=NR |
| F | MONALEESA-3 (ER ^f), Exploratory OS 56.3 months | | 134/237 (56.5) | 74/110 (67.3) | 39.7 (37.4, 46.9) | 33.7 (27.8, 41.3) | 0.78 (0.59, 1.04), p=NR |
| G | MONARCH 2 (ITT) 47.7 months | ABE + FUL vs. PBO + FUL | 211/446 (47.3) | 127/223 (57.0) | 46.7 | 37.3 | 0.76 (0.62, 0.95)^e , p=0.0139 |
| A vs. C | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, 44.8 months mFU) vs. MONALEESA-3 (ITT population, 39.4 months mFU) | | | | | | 1.13 (0.81, 1.58) p=0.4728 |
| A vs. D | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, 44.8 months mFU) vs. MONALEESA-3 (ER ^f , mFU 39.4 months) | | | | | | 1.12 (0.75, 1.65) p=0.5885 |
| A vs. E | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, 44.8 months mFU) vs. MONALEESA-3 (ITT population, 56.3 months mFU) Exploratory OS | | | | | | 1.11 (0.81, 1.53) p=0.522 |
| A vs. F | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population) vs. MONALEESA-3 (ER ^f , 56.3 months mFU) Exploratory OS | | | | | | 1.04 (0.72, 1.50) p=0.842 |
| B vs. C | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, 73.3 months mFU) vs. MONALEESA-3 (ITT population, 39.4 months mFU) | | | | | | 1.11 (0.83, 1.50) p=0.4908 |
| B vs. D | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, 73.3 months mFU) vs. MONALEESA-3 (ER ^f , 39.4 months mFU) | | | | | | 1.03 (0.73, 1.47) p=0.8556 |
| B vs. E | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, 73.3 months mFU) vs. MONALEESA-3 (ITT population, 56.3 months mFU) Exploratory OS | | | | | | 1.11 (0.82, 1.49) p=0.494 |
| B vs. F | Indirect comparison PAL+FUL vs. RIBO+FUL: PALOMA-3 (ITT population, 73.3 months mFU) vs. MONALEESA-3 (ER ^f , 56.3 months mFU) Exploratory OS | | | | | | 1.04 (0.73, 1.48) p=0.834 |
| A vs. G | Indirect comparison PAL+FUL vs. ABE+FUL: PALOMA-3 (ITT population, 44.8 months mFU) vs. MONARCH 2 (ITT population, 47.7 months mFU) | | | | | | 1.08 (0.78, 1.49), p=0.6595 |

Source: table constructed during the evaluation using information from Spreadsheets 'PFS & OS HR PAL_v_RIB' and 'PFS & OS HR PAL_v_ABE' in Excel workbook titled 'Attachment 4 Section 2 Indirect Treatment Comparisons', included as Attachment 4 of the submission; Table 15, p58 in Palbociclib (A5481023) CSR Main Body Abbreviated (data cut-off 13 April 2018), 19 September 2018; 'A5481026 – Updated OS TLS_Jan 2021' included as part of large files with the submission; Table 1, Figures 1A and 1C in Slamon 2020; Figures 1A and 1C in Slamon 2021; Sledge 2020; Table 7, Abemaciclib PSD, March 2021 PBAC Meeting.

ABE = abemaciclib; CI = confidence interval; ER = endocrine-resistant subgroup; FUL = fulvestrant; HR = hazard ratio; ITT = intention-to-treat; mFU = median follow-up; n = number of participants with event; N = total participants in group; NR = not reported; OS = overall survival; PAL = palbociclib; PBO = placebo; RIB = ribociclib

^a 50% quartile of Kaplan-Meier estimates of time to event (based on the Brookmeyer and Crowley Method).

^b Hazard ratio less than 1 is in favour of palbociclib plus fulvestrant.

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^c 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomisation.

^d Unplanned updated OS analysis performed in Q4 2020 with 393 events (75% of 521 total randomised patients) based on August 17, 2020 data cut-off in order to support country level HTA negotiations and provide more mature results as the study team prepares for final study closure.

^e Data were previously seen by the PBAC (MONALEESA-3: July 2020, November 2020 and March 2021 PBAC Meetings; MONARCH 2: March 2021 PBAC Meeting).

^f Patients who received trial treatment as second-line therapy or who had early relapse (within 12 months after completion of adjuvant or neoadjuvant endocrine therapy).

Bold indicates statistically significant results

- 6.20 All three placebo-controlled trials met their primary efficacy endpoint, demonstrating a statistically significant improvement in PFS with the addition of either palbociclib to fulvestrant (PALOMA-3), ribociclib to fulvestrant (MONALEESA-3), or abemaciclib to fulvestrant (MONARCH-2).
- 6.21 For PFS, the submission reported that the results of indirect comparison analyses were in favour of palbociclib over ribociclib, numerically, irrespective of whether the ITT population (indirect HR = 0.84; 95% CI 0.63, 1.13) or the endocrine-resistant subgroup (indirect HR = 0.87; 95% CI: 0.62, 1.23) of the MONALEESA-3 trial was used. The median PFS of the control group in the PALOMA-3 trial (4.6 months) was shorter than the median PFS of the control group in the MONALEESA-3 trial (12.8 months and 9.1 months for the ITT and endocrine-resistant subgroup respectively). The submission suggested the difference in median PFS between the two trials (shorter in PALOMA-3) was most likely explained by the inclusion of de novo metastatic disease in the MONALEESA-3 trial.
- 6.22 The submission reported that both the upper 95% CIs of the indirect estimates met a non-inferiority margin of 1.4. The submission noted a non-inferiority margin of 1.4 was previously accepted by the PBAC during consideration of palbociclib (paragraph 5.11, palbociclib PSD, March 2018) and abemaciclib for use in conjunction with a non-steroidal aromatase inhibitor (paragraph 6.13, abemaciclib PSD, March 2019) or with fulvestrant (paragraph 6.18, abemaciclib PSD, March 2021) in HR+/HER2- advanced breast cancer.
- 6.23 There was statistically significant improvement in median OS with the treatment groups in the MONARCH 2 (9.5 months, favouring abemaciclib group, ITT population) and MONALEESA-3 trial (favouring ribociclib group, ITT population) but not in the PALOMA-3 trial (6.9 months, favouring palbociclib).
- 6.24 For OS, the submission reported that the results of indirect comparison analyses were numerically in favour of ribociclib over palbociclib when considering the ITT populations of the PALOMA-3 (at median 73 months follow-up) and the MONALEESA-3 (at median 56 months follow-up) trials (indirect HR = 1.11; 95% CI: 0.82, 1.50). However, when the endocrine-resistant subgroup of the MONALEESA-3 trial was used, the submission reported that palbociclib and ribociclib had similar effectiveness in OS, as the indirect HR estimate was close to 1 (indirect HR = 1.04; 95% CI: 0.73, 1.48). The submission reported that both of the upper 95% CIs were marginally higher than the

non-inferiority margin of 1.4. The Pre-Sub-Committee Response (PSCR) noted that for the comparison between abemaciclib plus fulvestrant and ribociclib plus fulvestrant, the non-inferiority margin of 1.4 was also not met for OS in the ITT (upper 95% CI = 1.46) and ER (upper 95% CI = 1.52) populations. The PSCR stated that the non-inferiority of abemaciclib to ribociclib was accepted by the PBAC.

6.25 Several factors may potentially violate the transitivity assumption of the indirect comparisons, including:

- Different eligibility criteria and patient baseline characteristics, e.g. 21% of the patients in the PALOMA-3 trial were pre/perimenopausal compared to 0% and 18% in the MONALEESA-3 and MONARCH 2 trials respectively;
- Different prior therapies, e.g. all patients in the PALOMA-3 trial received prior endocrine therapy for primary diagnosis (60% more than one regimen) but half of the patients (51%) in the MONALEESA-3 trial were treatment-naïve. More than two-thirds (70%) of the patients in the MONARCH 2 trial received a prior aromatase inhibitor. One-third of the patients in the PALOMA-3 trial received previous chemotherapy in the advanced/metastatic setting but none in the other two comparator trials;
- Different post-discontinuation subsequent therapies. The direction and magnitude of any bias due to imbalances in subsequent treatments for palbociclib plus fulvestrant vs. ribociclib plus fulvestrant is not clear; and
- Varying duration of follow-up across trials, especially for PFS outcomes (median follow-up 15 months in the PALOMA-3 trial, versus 39.4 and 47.7 months in the MONALEESA-3 or MONARCH 2 trial respectively).

Comparative harms

6.26 The submission acknowledged that there were some differences in the safety profiles of palbociclib, ribociclib and abemaciclib. Table 7 presents a summary of selected treatment-emergent adverse events (TEAEs) in the included trials.

- In the PALOMA-3 trial, the most frequently (>25% of patients) reported treatment-related AEs in the palbociclib plus fulvestrant treatment group were neutropenia (84.1%), leukopenia (60.0%), infections (54.5%), fatigue (44.1%), nausea (35.9%), anaemia (31.6%), stomatitis (30.1%), diarrhoea (27.2%) and thrombocytopenia (25.5%), at a median follow-up of 44.8 months. The most frequent grade 3 or 4 AE was neutropenia (69.6%, palbociclib; 0%, placebo) and leukopenia (38.3%, palbociclib; 0.6%, placebo). The toxicity of palbociclib plus fulvestrant was manageable by dosing interruptions, dose reductions, and/or standard medical care.
- In the MONALEESA-3 trial, the most frequently reported TEAEs in the ribociclib plus fulvestrant arm were neutropenia (72.0%), infections (58.6%), leukopenia (32.5%) and diarrhoea (29.0%), at a median follow-up of 56.3 months. The most

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frequent grade 3 or 4 AE was neutropenia (58.2%, ribociclib; 0.8%, placebo). Grade 3 or 4 adverse events of special interest included hepatobiliary toxicity (13.9%, ribociclib; 6.2%, placebo) and prolonged QT interval (3.1%, ribociclib; 1.2%, placebo) (Slamon 2021).

- In the MONARCH 2 trial, the most frequently reported TEAEs in the abemaciclib plus fulvestrant arm were diarrhoea (87.1%), neutropenia (49.7%), nausea (49.2%), fatigue (42.9%), anaemia (34.7%) and leukopenia (33.1%), at a median follow-up of 47.7 months. The most frequent grade 3 or 4 AE was neutropenia (29.7%, abemaciclib; 1.8%, placebo), leukopenia (13.4%, abemaciclib; 0%, placebo) and diarrhoea (14.5%, abemaciclib; 0.4%, placebo).

6.27 Overall, the submission concluded that palbociclib plus fulvestrant is similar in terms of safety compared with ribociclib plus fulvestrant and abemaciclib plus fulvestrant.

Table 7: Selected TEAEs in the included trials

| TEAE | PALOMA-3 ^a (data cut-off 13 Apr 2018; median 44.8 months FU) | | MONALEESA-3 (data cut-off 30 Oct 2020; median 56.3 months FU, minimum 52.7 months) | | MONARCH 2 (data cut-off 20 Jun 2019) ^b median 47.7 months FU | |
|---------------------------|---|----------------------|---|----------------------|---|----------------------|
| | PAL + FUL (N=345) | PBO + FUL (N=172) | RIB + FUL (N=483) | PBO + FUL (N=241) | ABE + FUL (N=441) | PBO + FUL (N=223) |
| Any AEs (any CTCAE grade) | 341 (98.8) | 161 (93.6) | 473 (97.9) | 219 (90.9) | 435 (98.6) | 203 (91.0) |
| Grade 3+ | 278 (80.6) | 48 (27.9) | NR | NR | 291 (66.0) | 61 (27.4) |
| Neutropenia | 290 (84.1) | 6 (3.5) | 348 (72.0) | 9 (3.7) | 219 (49.7) | 9 (4.0) |
| Grade 3+ | 240 (69.6) | 0 (0) | 281 (58.2) | 2 (0.8) | 131 (29.7) | 4 (1.8) |
| Leukopenia | 207 (60.0) | 9 (5.2) | 157 (32.5) | 4 (1.7) | 146 (33.1) | 4 (1.8) |
| Grade 3+ | 132 (38.3) | 1 (0.6) | 82 (17.0) | 0 (0) | 59 (13.4) | 0 (0) |
| Infections | 188 (54.5) | 60 (34.9) | 283 (58.6) | 108 (44.8) | NR | NR |
| Fatigue | 152 (44.1) | 54 (31.4) | NR | NR | 189 (42.9) | 64 (28.7) |
| Nausea | 124 (35.9) | 53 (30.8) | NR | NR | 217 (49.2) | 56 (25.1) |
| Anaemia | 109 (31.6) | 24 (14.0) | 97 (20.1) | 21 (8.7) | 153 (34.7) | 10 (4.5) |
| Grade 3+ | 15 (4.3) | 4 (2.3) | NR | NR | 40 (9.1) | 3 (1.3) |
| Stomatitis | 104 (30.1) | 24 (14.0) | NR | NR | 77 (17.5) | 24 (10.8) |
| Diarrhoea | 94 (27.2) | 35 (20.3) | 140 (29.0) | 49 (20.3) | 384 (87.1) | 62 (27.8) |
| Grade 3+ | 0 | 2 (1.2) | NR | NR | 64 (14.5) | 1 (0.4) |
| Thrombocytopenia | 88 (25.5) | 0 (0) | 45 (9.3) | 6 (2.5) | 77 (17.5) | 6 (2.7) |
| AST increased | 40 (11.6) | 13 (7.6) | NR | NR | 69 (15.6) | 16 (7.2) |
| ECG QT prolonged | 1 (0.3) | 0 (0) | 41 (8.5) | 5 (2.1) | 0 | 0 |
| TEAE (any CTCAE grade) | Indirect comparison RR (indirect, IV, random) (95% CI) | | | | | |
| | PAL vs. RIB | | | PAL vs. ABE | | |
| Any TEAE | 0.98 (0.92, 1.04) | | | 0.97 (0.92, 1.03) | | |
| Neutropenia | 1.25 (0.45, 3.45) | | | 1.96 (0.71, 5.4) | | |
| Leukopenia | 0.59 (0.18, 1.89) | | | 0.62 (0.19, 2.00) | | |
| Anaemia | 0.98 (0.54, 1.79) | | | 0.29 (0.14, 0.61) | | |
| Diarrhoea | 0.74 (0.48, 1.16) | | | 0.43 (0.29, 0.64) | | |
| ECG QT prolonged | 0.37 (0.01, 10.18) | | | - | | |

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Source: Excel workbook 'Attachment 4 Section 2 Indirect Treatment Comparison' of the submission; Table 24, pp77-78 in Palbociclib (A5481023) CSR Main Body Abbreviated (data cut-off 13 April 2018), 19 September 2018; Supplementary Table 2 in Slamon 2021; eTable 2 in Supplement 2 of Sledge 2020

ABE = abemaciclib; AE = adverse event; AST = Aspartate Aminotransferase; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FU = follow-up; FUL = fulvestrant; IV = inverse variance; PAL = palbociclib; PBO = placebo; n = number of patients with event; N = number of total participants in group; NR = not reported; PAL = palbociclib; RIB = ribociclib; TEAE = treatment-emergent adverse event

^a TEAEs in $\geq 10\%$ of patients in either treatment group by CTCAE grade (all-causality, all cycles) in the PALOMA-3 trial.

^b Data were previously seen by the PBAC (MONARCH 2: March 2021 PBAC Meeting).

Benefits/harms

6.28 A benefits/harms table has not been presented as the clinical claim was of non-inferiority.

Clinical claim

6.29 The submission described palbociclib plus fulvestrant as non-inferior in terms of efficacy to ribociclib plus fulvestrant and to abemaciclib plus fulvestrant, in patients with HR+/HER2– inoperable locally advanced or metastatic breast cancer previously treated with endocrine therapy.

6.30 The PBAC considered that the claims of non-inferiority in terms of comparative clinical effectiveness between palbociclib plus fulvestrant and (i) ribociclib plus fulvestrant and (ii) abemaciclib plus fulvestrant were supported, noting that:

- Several factors may have violated the transitivity assumptions underlying the indirect comparisons (e.g. different eligibility criteria, patient baseline characteristics, prior therapies, post-discontinuation subsequent therapies and durations of follow-up, especially for PFS outcomes).
- Although all upper 95% confidence intervals of the indirect comparison hazard ratios for PFS were within the proposed non-inferiority margin of 1.4, none were within the margin for OS. The PSCR noted that PBAC previously accepted non-inferiority for abemaciclib plus fulvestrant to ribociclib plus fulvestrant based on an indirect comparison where the 95% confidence intervals for OS also exceeded a non-inferiority margin of 1.4 (ITT population: upper 95% CI = 1.46; endocrine resistant subgroup: upper 95% CI = 1.52).

6.31 The submission described palbociclib plus fulvestrant as similar in terms of safety to ribociclib plus fulvestrant and to abemaciclib plus fulvestrant, in patients with HR+/HER2– inoperable locally advanced or metastatic breast cancer previously treated with endocrine therapy. The PBAC considered that this was reasonable.

Economic analysis

6.32 The submission adopted a cost-minimisation approach (CMA) on the basis that palbociclib plus fulvestrant is non-inferior to ribociclib plus fulvestrant in terms of efficacy and similar in terms of safety.

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- 6.33 The submission requested the same effective AEMP for palbociclib as ribociclib at equi-effective doses. This price in turn would be the same as the current effective AEMP for palbociclib when used in combination with an NSAID (see Table 8).
- 6.34 The submission proposed that the equi-effective doses for the existing listing of palbociclib in combination with a NSAID and ribociclib in combination with a NSAID be applied to the CMA for palbociclib in combination with fulvestrant and ribociclib in combination with fulvestrant. The ESC noted that this was consistent with the approach accepted by the PBAC in the consideration of ribociclib plus fulvestrant versus ribociclib plus NSAID as first-line treatment in the metastatic setting at the July 2020 PBAC meeting at which the ESC and the PBAC considered that “there did not appear to be a clinical reason why dose intensities for ribociclib would differ depending on its combination with fulvestrant or NSAID, given the similar safety profiles of RIBO+FULV and RIBO+NSAI” (paragraph 6.54, ribociclib PSD, July 2020).
- 6.35 Therefore, the proposed equi-effective doses, which were calculated based on the mean relative dose intensities (RDIs) of palbociclib (86.8%) and ribociclib (79.5%) from the PALOMA-2 and MONALEESA-2 trials respectively and which were the same as accepted by the PBAC in the consideration of palbociclib + NSAID, were:

Palbociclib 108.5 mg = ribociclib 477 mg per day for 21 days of a 28-day cycle (i.e. Palbociclib 1 mg = ribociclib 4.40 mg)

Table 8: CMA between ribociclib and palbociclib

| | Ribociclib | Source |
|-------------------------------|-------------------------------------|--|
| Effective AEMP | \$ [REDACTED] (21 x 200 mg tablets) | Submission was aware of the effective AEMP of ribociclib due to existing RSA |
| Daily dose | 477 mg | Equi-effective doses |
| Cost per day | \$ [REDACTED] | = \$ [REDACTED] / 200 mg / 21 tablets * 477 mg |
| | Palbociclib | |
| Daily dose | 108.5 mg | Equi-effective doses |
| Cost per day | \$ [REDACTED] | From above |
| Cost per 21 days ^a | \$ [REDACTED] | = \$ [REDACTED] x 21 days |

Source: Attachment 5 Section 3 CMA.xlsx

AEMP = approved ex-manufacturer price

^a Palbociclib has a flat pricing structure for the 75 mg, 100 mg and 125 mg tablets

- 6.36 The ESC noted that the proposed price is consistent with previous PBAC considerations that the price of ribociclib or abemaciclib, when used in combination with fulvestrant, should not be higher than the price of the drug when used in combination with an NSAID (paragraph 5.9, ribociclib PSD, November 2020; paragraph 6.45, abemaciclib PSD, March 2021).
- 6.37 A sensitivity analysis was performed which estimated the equi-effective doses using the RDIs of palbociclib and ribociclib from the PALOMA-3 and MONALEESA-3 trials (i.e. when used in combination with fulvestrant). This resulted in equi-effective doses of:
Palbociclib 105.9 mg = ribociclib 511.2 mg per day for 21 days of a 28-day cycle (i.e. Palbociclib 1 mg = ribociclib 4.83 mg)

- 6.38 The trials informing these doses were not completely matched: 19% of patients in the MONALEESA-3 trial had de novo disease versus no patients in PALOMA-3, and dose intensity data were not available specifically for the endocrine-resistant subgroup in MONALEESA-3, which was relevant to the current submission.
- 6.39 The ESC noted that use of these doses would result in a higher AEMP for palbociclib which was inconsistent with the PBACs previous recommendations (see paragraph 6.33). In addition, the ESC noted that, that in context with the cost minimisation approach and as per Section 101(3B) of the National Health Act 1953, the price of palbociclib when used in combination with fulvestrant or a NSAID should be no higher than the prices for the existing listings of ribociclib or abemaciclib when used in combination fulvestrant.

Drug cost/patient/script

- 6.40 The proposed price for palbociclib when use in combination with fulvestrant is the same as the current price for palbociclib when use in combination with a NSAID (i.e. effective AEMP = \$1 per 21 x 75 mg, 100 mg or 125 mg tablets).

Estimated PBS usage & financial implications

- 6.41 This submission was not considered by DUSC.
- 6.42 The submission adopted an epidemiological approach to estimate the number of patients eligible for the proposed treatment. A market share approach was not adopted as there were insufficient ribociclib plus fulvestrant data available at the time of submission (ribociclib plus fulvestrant was PBS listed 1 April 2021). Table presents the key inputs for the utilisation and financial estimates.

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Table 9: Key inputs for financial estimates

| Data | Value | Source | Comments |
|---|--|---|--|
| Eligible population | | | |
| Eligible patients | Year 1: █████ ¹ Year 2: █████ ¹ Year 3: █████ ¹ Year 4: █████ ¹ Year 5: █████ ¹ Year 6: █████ ¹ | Submission | The ESC considered that the eligible patient population was likely underestimated. |
| Grandfather patients | Year 1: █████ ² | Number of patients currently on sponsor's compassionate access program who will be grandfathered onto the PBS. | - |
| Treatment utilisation | | | |
| Proportion of eligible patients electing palbociclib plus fulvestrant | Year 1: 27% Year 2: 53% Years 3-6: 54% | Market share assumptions for palbociclib: based on PBS services for ribociclib, palbociclib and abemaciclib at August 2019, August 2020 and August 2021 | Years 1 and 2 market share based on the % of PBS services in August 2019 (fourth month of listing of PAL+NSAI) and August 2020. The submission assumed that the market share of PAL+NSAI would equal the market share of PAL+FUL. Year 3 market share of PAL+NSAI may be an underestimate as the RIB utilisation data included RIB+FUL (listed from 1 April 2021) (RIB/PAL/ABE 40%/54%/6% in August 2021). Years 4-6: assumed constant |
| Duration of treatment - palbociclib | 466.6 days | Mean duration of treatment with PAL + FUL in PALOMA-3 (PALOMA-3 CSR, 13 April 2018, Table 21). | Used to estimate the number of scripts required (treatment days: Year 1 = 365.25; Year 2 = 101.35) This treatment duration has also been assumed for ribociclib. |
| Distribution of palbociclib scripts | 125 mg: 57% 100 mg: 14% 75 mg: 29% | PBS statistics for current palbociclib listing (May 19 – Sep 21) | Based on this distribution the average dose is approximately 107 mg (0.57 x 125 mg + 0.14 x 100 mg + 0.29 x 75 mg). This is similar to the average daily dose on which the equi-effective doses are based (108.5 mg). |
| Compliance – palbociclib | 86.8% | Mean RDI from PALOMA-2 (PALOMA-2 CSR, Table 35) | The submission inappropriately applied the RDI assuming it reflected 'adherence'. This incorrectly reduced the average daily dose to 92.9mg (108.5 mg x 0.868). The pre-PBAC response acknowledged this error. |
| Distribution of ribociclib scripts | 3 x 200 mg: 61% 2 x 200 mg: 31% 1 x 200 mg: 7% | PBS statistics for current ribociclib listing (May 19 – Sep 21) | Based on this distribution the average dose is approximately 504 mg (0.61 x 600 mg + 0.31 x 400 mg + 0.07 x 200 mg). This is higher than the average daily dose on which the equi-effective doses are based (477 mg). |
| Compliance – ribociclib | 79.5% | Mean RDI from MONALEESA-2 (para. 6.36, Abemaciclib PSD, March 2021 PBAC Meeting) | The submission inappropriately applied the RDI assuming it reflected 'adherence'. This incorrectly reduced the average daily dose to 401 mg (504 mg x 0.795). The pre-PBAC response acknowledged this error. |
| Costs | | | |

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| Data | Value | Source | Comments |
|-------------------|----------------------------|-------------------------------|---|
| Patient copayment | PBS \$19.81 RPBS \$4.63 | PBS statistics for ribociclib | - |
| MBS costs | \$26.04 | 80% of fee for MBS item 11704 | 85% benefit (\$27.70) should have been applied (low financial impact) |

Source: Table 4.1.1, pp246-247 of the submission

CSR = Clinical Study Report; ESC = Economic Sub-Committee; FUL = fulvestrant; MBS = Medical Benefits Schedule; NSAI = non-steroidal aromatase inhibitor; PAL = palbociclib; PBS = Pharmaceutical Benefits Schedule; PSD = Public Summary Document; RIB = ribociclib; RDI = relative dose intensity

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

6.43 ² < 500 Table 210 presents the estimated use and financial implications of listing palbociclib in combination with fulvestrant on the PBS corrected for compliance of both palbociclib and ribociclib.

Table 20: Corrected estimations use and financial implications (effective prices)

| | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 |
|--|------------------|------------------|------------------|------------------|------------------|------------------|
| Patients treated | ¹ | ¹ | ¹ | ¹ | ¹ | ¹ |
| Palbociclib scripts dispensed ^a | ² | ² | ⁵ | ⁵ | ⁵ | ⁵ |
| Ribociclib scripts not dispensed ^b | ² | ² | ⁵ | ⁵ | ⁵ | ⁵ |
| Estimated financial implications of palbociclib | | | | | | |
| Cost to PBS/RPBS less copayments | \$ ³ | \$ ³ | \$ ³ | \$ ³ | \$ ³ | \$ ³ |
| Estimated financial implications for ribociclib | | | | | | |
| Cost to PBS/RPBS less copayments | \$ ³ | \$ ³ | \$ ³ | \$ ³ | \$ ³ | \$ ³ |
| Net financial implications | | | | | | |
| Net cost to PBS/RPBS | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ |
| Net cost to MBS | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ |
| Net cost to PBS/RPBS/MBS | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ | -\$ ⁴ |

^a Assuming 11.32 scripts per year in the initial year and 3.13 in subsequent years as estimated by the submission. Calculation incorrect, corrected to 13.04 scripts per patient in revised calculations.

^b Assuming 10.36 scripts per year in the initial year and 2.87 in subsequent years as estimated by the submission. Calculation incorrect, corrected to 13.04 scripts per patient in revised calculations.

Source: Tables 4.2.6, 4.2.7 and 4.5.3, pp256-257 and 265 of the submission.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ net cost saving

⁵ 5,000 to < 10,000

6.44 The submission underestimated the number of prescriptions for both palbociclib and ribociclib due to incorrectly assuming that the RDI reflected adherence. The RDI reflects dose reductions which are accounted for with the use of lower strength tablets (for palbociclib) or lower quantities (for ribociclib). The pre-PBAC response acknowledged this error and accepted the corrected estimates presented in Table 10.

6.45 For palbociclib the assumed distribution of use was 57% use of 125 mg, 14% use of 100 mg and 29% use of 75mg tablets, resulting in an average dose of approximately

107 mg. This is similar to the average daily dose on which the equi-effective doses are based (108.5 mg). For ribociclib the assumed distribution of use was 61% use of 600 mg, 31% use of 400 mg and 7% use of 200 mg tablets, resulting in an average dose is approximately 504 mg. This is higher than the average daily dose on which the equi-effective doses are based (477 mg).

- 6.46 Removing the ‘adherence’ adjustment, the saving to the PBS/RPBS (effective prices) was estimated to be net cost saving in Year 6, and net cost saving over the first 6 years of listing. The savings reflect that the average dose of ribociclib, and hence the cost offsets for ribociclib, were overestimated. Reducing the dose of ribociclib to be consistent with that assumed for the equi-effective doses would result in the listing of palbociclib being cost neutral. The pre-PBAC response stated that PBS statistics indicated that the average daily dose of palbociclib was slightly lower and the average daily dose of ribociclib was slightly higher than the average daily doses on which the equi-effective doses were based. The pre-PBAC response stated that if the current pattern of use for palbociclib and ribociclib remained the same, then the PBS listing of palbociclib would be cost saving rather than cost neutral.
- 6.47 The submission assumed no market growth with the listing of palbociclib in combination with fluevestrant. This was reasonable given this will be the third CDK 4/6 inhibitor listed on the PBS.
- 6.48 The submission included MBS cost-savings associated with reduced cardiac monitoring from substitution of ribociclib with palbociclib.
- 6.49 < 500 grandfathered patients were included in the estimated number of patients in Year 1.

Quality Use of Medicines

- 6.50 The submission reported the following activities to support the quality use of medicines:
- Provision of educational materials (Product Information, information on the safety and efficacy of palbociclib, Patient Management Guide, educational programs for oncologists) to healthcare professionals;
 - Provision of Consumer Medicine Information and patient information booklets to patients;
 - Engagement with relevant stakeholders, e.g., the Medical Oncology Group of Australia and the Breast Cancer Network of Australia.

Financial Management – Risk Sharing Arrangements

- 6.51 The submission requested that the proposed extended listing of palbociclib, for use in combination with fulvestrant, be included in the existing RSA that palbociclib currently shares with ribociclib and abemaciclib. The ESC considered that this would be

appropriate and align with the PBAC recommendations for ribociclib and abemaciclib plus fulvestrant.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of palbociclib, in combination with fulvestrant, for the treatment of patients with locally advanced (stage IIIB/IIIC) or metastatic (stage IV) hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer who have received previous endocrine therapy. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost minimisation approach between palbociclib plus fulvestrant and ribociclib and fulvestrant was acceptable and that the listing should result in no net cost to Government.
- 7.2 The PBAC noted that the Medical Oncology Group of Australia supported the listing of palbociclib plus fulvestrant on the PBS for the treatment of breast cancer.
- 7.3 The PBAC noted that the proposed restriction for palbociclib plus fulvestrant was slightly narrower than the current PBS-listed populations for ribociclib plus fulvestrant and abemaciclib plus fulvestrant. Ribociclib or abemaciclib plus fulvestrant may be used in patients who have not been treated with endocrine therapy for advanced/metastatic disease; whereas, the proposed restriction for palbociclib plus fulvestrant does not allow use in these patients. The PBAC considered that this difference in the proposed restriction was reasonable as it aligned with the PALOMA-3 trial and the TGA indication for palbociclib. The PBAC advised that the existing restrictions for palbociclib for use in combination with non-steroidal aromatase inhibitors (NSAIs; initial and continuing) should be amended to allow combination use with fulvestrant and to otherwise align with those for ribociclib and abemaciclib.
- 7.4 The PBAC advised that flow on restriction changes would be required for ribociclib and abemaciclib to prevent the sequential use of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors.
- 7.5 The PBAC also advised that a grandfather listing be implemented.
- 7.6 The PBAC considered that the proposed place in therapy was appropriate and aligned with that of the nominated comparator, ribociclib plus fulvestrant. The PBAC considered that abemaciclib plus fulvestrant was a secondary comparator.
- 7.7 The PBAC noted that the submission was based on indirect treatment comparisons (ITCs) between palbociclib plus fulvestrant (PALOMA-3 trial) and (i) ribociclib plus fulvestrant (MONALEESA-3 trial) and (ii) abemaciclib plus fulvestrant (MONARCH 2 trial) using placebo plus fulvestrant as the common treatment arm.

- 7.8 The PBAC considered that the PALOMA-3, MONALEESA-3 and MONARCH 2 trials were similar, noting that there were differences in terms of the key eligibility criteria (see paragraph 6.10) and subsequent therapies and durations of follow-up (see paragraph 6.11). The PBAC noted that the upper 95% confidence intervals of the indirect hazard ratios for progression free survival were within the proposed non-inferiority margin of 1.4. The PBAC noted that although the upper 95% confidence intervals for overall survival were outside the nominated non-inferiority margin, similar results were observed in the March 2021 consideration of abemaciclib when compared to ribociclib. Overall, the PBAC considered that the claim that palbociclib plus fulvestrant was non-inferior to ribociclib plus fulvestrant in terms of efficacy was supported by the evidence presented.
- 7.9 The PBAC, noting that the safety profiles had some differences, considered that overall, the claim that palbociclib plus fulvestrant had a similar safety profile to ribociclib plus fulvestrant was supported by the evidence presented.
- 7.10 The PBAC noted that the submission presented a cost minimisation approach between palbociclib plus fulvestrant and ribociclib plus fulvestrant. The PBAC noted that as there were no significant differences in efficacy or safety the submission did not include any additional costs in the CMA. The PBAC considered this was reasonable. The PBAC considered that the equi-effective doses were:
- Palbociclib 108.5 mg = ribociclib 477 mg per day for 21 days of a 28-day cycle (i.e. palbociclib 1 mg = ribociclib 4.4 mg)
- 7.11 The PBAC noted that the equi-effective doses were the same as those accepted previously for the comparison between palbociclib plus an NSAID and ribociclib plus an NSAID. The PBAC recalled that this was consistent with the approach that was accepted in the consideration of ribociclib plus fulvestrant when the PBAC considered that there did not appear to be a clinical reason why the dose intensities for ribociclib would differ depending on its combination with fulvestrant or an NSAID given the similar safety profiles (paragraph 6.54, ribociclib PSD, July 2020).
- 7.12 The PBAC noted that the proposed price for palbociclib for use in combination with fulvestrant was the same as that for palbociclib for use in combination with an NSAID. Consistent with its recommendations for ribociclib (November 2020) and abemaciclib (March 2021), the PBAC advised that the price of palbociclib, when used in combination with fulvestrant, should not be higher than the price for the existing listing of palbociclib when used in combination with an NSAID. The PBAC considered for the purpose of Section 101(3B) of the National Health Act 1953, that ribociclib and abemaciclib were alternate therapies to palbociclib, and that palbociclib does not provide a significant improvement in efficacy and/or reduction of toxicity over these alternative therapies. The price of palbociclib when used in combination with fulvestrant should therefore be no higher than the price of either ribociclib or abemaciclib when used in combination with fulvestrant.

- 7.13 The PBAC noted that the corrected utilisation and financial estimates resulted in a net cost saving to Government over the first six years of listing. The PBAC noted that the pre-PBAC response stated that this was due to PBS statistics indicating that the actual average daily dose of palbociclib was slightly lower and the actual average daily dose of ribociclib was slightly higher than the equi-effective doses applied in the cost minimisation. The PBAC also noted that the submission included MBS cost-savings associated with reduced cardiac monitoring from the substitution of ribociclib with palbociclib. The PBAC considered that this was inconsistent with the CMA approach applied. The PBAC considered that the listing of palbociclib should result in no net cost to Government.
- 7.14 The PBAC advised that palbociclib, when used in combination with fulvestrant, should be included in the existing risk sharing arrangement that palbociclib currently shares with ribociclib and abemaciclib.
- 7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because palbociclib, when used in combination with fulvestrant, is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over ribociclib or abemaciclib plus fulvestrant, or 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 2009* for Pricing Pathway A were not met.
- 7.16 The PBAC noted that this submission was not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|--|---------------|-------------------|-------------------|--|---------------------|
| PALBOCICLIB | | | | | |
| palbociclib 125 mg tablet, 21 | 12822W | 1 | 21 | 5 | Ibrance |
| palbociclib 100 mg tablet, 21 | 12819Q | 1 | 21 | 5 | Ibrance |
| palbociclib 75 mg tablet, 21 | 12818P | 1 | 21 | 5 | Ibrance |
| | | | | Max. Qty multiplier = 1; Repeat increases: nil | |
| Edit existing Restriction Summary / ToC: | | | | | |
| Category / Program: GENERAL – General Schedule (Code GE) | | | | | |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | | |
| Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia | | | | | |
| Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS | | | | | |

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| | |
|--|---|
| | 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: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors for the purposes of this restriction are abemaciclib, palbociclib and ribociclib |
| | Administrative Advice: Non-steroidal aromatase inhibitors for the purposes of this restriction are anastrozole and letrozole |
| | Indication: Locally advanced or metastatic breast cancer |
| | Treatment Phase: Initial treatment |
| | Clinical criteria: Patient must be untreated with a cyclin-dependent kinase 4 and 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 be hormone receptor positive |
| | AND |
| | Clinical criteria: The condition must be human epidermal growth factor receptor 2 (HER2) negative |
| | AND |
| | Clinical criteria: The condition must be inoperable |
| | AND |
| | Clinical criteria: Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less |
| | AND |
| | Clinical criteria: The treatment must be in combination, where the patient has never been treated with endocrine therapy for advanced/metastatic disease, with a non-steroidal aromatase inhibitor; OR |
| | The treatment must be in combination, where the patient has recurrence/progressive disease despite being treated with endocrine therapy in the (neo)adjuvant setting for advanced/metastatic disease, with fulvestrant only |
| | AND |
| | Clinical criteria: The treatment must not be in combination with another cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy |
| | Population criteria: Patient must not be premenopausal |
| Edit Restriction Summary / ToC: to appear as follows: | |
| | Indication: Locally advanced or metastatic breast cancer |
| | Treatment Phase: Continuing treatment |
| | Clinical criteria: |

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| | |
|--|---|
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition |
| | AND |
| | Clinical criteria: |
| | Patient must not have developed disease progression while being treated with this drug for this condition |
| | AND |
| | Clinical criteria: |
| | The treatment must be in combination with one of: (i) non-steroidal aromatase inhibitor, (ii) fulvestrant |
| | AND |
| | Clinical criteria: |
| | The treatment must not be in combination with another cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy |
| | AND |
| | Population criteria: |
| | Patient must not be premenopausal |
| Add Restriction Summary: / ToC: | |
| | Category / Program: GENERAL – General Schedule (Code GE) |
| | Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners |
| | Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia |
| | Indication: Locally advanced or metastatic breast cancer |
| | Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - 'Grandfather' arrangements |
| | Clinical criteria: |
| | Patient must have received treatment with this drug for this PBS-indication prior to [insert date of PBS listing] |
| | AND |
| | Clinical criteria: |
| | Patient must not have developed disease progression while being treated with this drug for this condition |
| | AND |
| | Clinical criteria: |
| | Patient must have been untreated with a cyclin-dependent kinase 4 and 6 (CDK4/6) at the time non-PBS supply was initiated; 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 be hormone receptor positive |
| | AND |
| | Clinical criteria: |
| | The condition must be human epidermal growth factor receptor 2 (HER2) negative |
| | AND |
| | Clinical criteria: |
| | The condition must be inoperable |
| | AND |
| | Clinical criteria: |
| | Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 2 at the time of non-PBS supply was initiated |
| | AND |

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| | |
|--|--|
| | Clinical criteria: |
| | The treatment must be in combination with fulvestrant only, where at the time non-PBS supply was initiated, the patient had recurrent/progressive disease despite being treated with endocrine therapy in the (neo)adjuvant setting or for advanced/metastatic disease |
| | AND |
| | Clinical criteria: |
| | The treatment must not be in combination with another cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy |
| | AND |
| | Population criteria: |
| | Patient must not be premenopausal |
| | Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| | Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |

8.2 Amend existing ribociclib and abemaciclib listings as follows to prevent sequential use of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors.

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|---|---------------|-------------------|-------------------|--|---------------------|
| RIBOCICLIB | | | | | |
| ribociclib 200 mg tablet, 21 | 11385F | 1 | 21 | 5 | Kisqali |
| ribociclib 200 mg tablet, 42 | 11397W | 1 | 21 | 5 | Kisqali |
| ribociclib 200 mg tablet, 63 | 11386G | 1 | 21 | 5 | Kisqali |
| | | | | Max. Qty multiplier = 1; Repeat increases: nil | |
| MEDICINAL PRODUCT medicinal product pack | | | | | |
| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
| ABEMACICLIB | | | | | |
| abemaciclib 150 mg tablet, 56 | 11868P | 1 | 21 | 5 | Verzenio |
| abemaciclib 100 mg tablet, 56 | 11871T | 1 | 21 | 5 | Verzenio |
| abemaciclib 50 mg tablet, 56 | 11876C | 1 | 21 | 5 | Verzenio |
| | | | | Max. Qty multiplier = 1; Repeat increases: nil | |
| Edit existing Restriction Summaries / ToCs to appear as follows: | | | | | |
| Category / Program: GENERAL – General Schedule (Code GE) | | | | | |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | | |
| Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia | | | | | |
| 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: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors for the purposes of this restriction are abemaciclib, palbociclib and ribociclib | | | | | |

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| | Administrative Advice: Non-steroidal aromatase inhibitors for the purposes of this restriction are anastrozole and letrozole |
| | Indication: Locally advanced or metastatic breast cancer |
| | Treatment Phase: Initial treatment |
| | Clinical criteria: |
| | Patient must be untreated with a cyclin-dependent kinase 4 and 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 be hormone receptor positive |
| | AND |
| | Clinical criteria: |
| | The condition must be human epidermal growth factor receptor 2 (HER2) negative |
| | AND |
| | Clinical criteria: |
| | The condition must be inoperable |
| | AND |
| | Clinical criteria: |
| | Patient must have a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less |
| | AND |
| | Clinical criteria: |
| | The treatment must be in combination, where the patient has never been treated with endocrine therapy for advanced/metastatic disease, with one of (i) a non-steroidal aromatase inhibitor, (ii) fulvestrant; OR |
| | The treatment must be in combination, where the patient has recurrence/progressive disease despite being treated with endocrine therapy for advanced/metastatic disease, with fulvestrant only |
| | AND |
| | Clinical criteria: |
| | The treatment must not be in combination with another cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy |
| | Population criteria: |
| | Patient must not be premenopausal |
| Edit Restriction Summaries / ToCs to appear as follows: | |
| | Indication: Locally advanced or metastatic breast cancer |
| | Treatment Phase: Continuing treatment |
| | Clinical criteria: |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition |
| | AND |
| | Clinical criteria: |
| | Patient must not have developed disease progression while being treated with this drug for this condition |
| | AND |
| | Clinical criteria: |
| | The treatment must be in combination with one of: (i) non-steroidal aromatase inhibitor, (ii) fulvestrant |
| | AND |
| | Clinical criteria: |

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| | |
|--|---|
| | The treatment must not be in combination with another cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy |
| | AND |
| | Population criteria: |
| | Patient must not be premenopausal |
| Edit Restriction Summaries / ToCs to appear as follows: | |
| | Category / Program: GENERAL – General Schedule (Code GE) |
| | Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners |
| | Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia |
| | Indication: Locally advanced or metastatic breast cancer |
| | Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - 'Grandfather' arrangements |
| | Clinical criteria: |
| | Patient must have received treatment with this drug for this PBS-indication prior to [insert date of PBS listing] |
| | AND |
| | Clinical criteria: |
| | Patient must not have developed disease progression while being treated with this drug for this condition |
| | AND |
| | Clinical criteria: |
| | Patient must have been untreated with a cyclin-dependent kinase 4 and 6 (CDK4/6) at the time non-PBS supply was initiated; 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 be hormone receptor positive |
| | AND |
| | Clinical criteria: |
| | The condition must be human epidermal growth factor receptor 2 (HER2) negative |
| | AND |
| | Clinical criteria: |
| | The condition must be inoperable |
| | AND |
| | Clinical criteria: |
| | Patient must have had a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score no higher than 2 at the time of non-PBS supply was initiated |
| | AND |
| | Clinical criteria: |
| | The treatment must be in combination with one of (i) a non-steroidal aromatase inhibitor, (ii) fulvestrant, where the patient has never been treated with endocrine therapy for advanced/metastatic disease at the time non-PBS supply was initiated OR |
| | Clinical criteria: |
| | The treatment must be in combination with fulvestrant only, where at the time non-PBS supply was initiated, the patient had recurrent/progressive disease despite being treated with endocrine therapy for advanced/metastatic disease |
| | AND |

| | |
|--|--|
| | Clinical criteria: |
| | The treatment must not be in combination with another cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy |
| | AND |
| | Population criteria: |
| | Patient must not be premenopausal |
| | Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| | Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |

This restriction may be subject to further review. Should there be any changes made to the restriction 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.