7.02 ELACESTRANT,
Tablet 86 mg (as dihydrochloride),
Tablet 345 mg (as dihydrochloride),
Orserdu®
A.Menarini Australia Pty Ltd

1 Purpose of submission

1.1 A standard re-entry integrated codependent resubmission requesting MBS listing of testing for activating estrogen receptor 1 *(ESR1)* variants in circulating tumour DNA (ctDNA) extracted from blood plasma (liquid biopsy) and PBS listing of elacestrant for the targeted treatment of estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-), locally advanced or metastatic breast cancer (mBC), in patients who have disease progression following at least one line of endocrine therapy (ET), including a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) for ≥ 12 months and who test positive for an activating *ESR1* variant. The first submission was considered at the March 2025 PBAC meeting.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus everolimus + exemestane (EVE + EXE) (Table 1).

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

Component	Description
Population	Test: Men and postmenopausal women with ER+/HER2- mBC, who have disease progression following at least one line of ET, including a CDK4/6i for ≥12 months. Drug: Men and postmenopausal women with ER+/HER2- mBC, who have disease progression following at least one line of ET, including a CDK4/6i for ≥12 months and test positive for an activating ESR1 variant.
Intervention	Test: Testing for *ESR1* variants in ctDNA extracted from blood (liquid biopsy). Drug: Elacestrant 345mg po daily until disease progression or unacceptable toxicity
Comparator	Test: No testing Drug: SOC 2L treatment – nominated as EVE + EXE (an oral regimen of EVE 10mg per day plus EXE 25mg per day until disease progression or unacceptable toxicity).
Outcomes	Test outcomes have previously been evaluated are not represented in this resubmission. Drug: OS, PFS, HRQoL, AEs
Clinical claim	In men and postmenopausal women with ER+/HER2- mBC, who have disease progression following at least one line of ET, including a CDK4/6i for ≥12 months, with *ESR1* variant identified by testing of ctDNA extracted from blood (liquid biopsy), elacestrant is superior in terms of efficacy and likely better tolerated, compared to EVE + EXE.

Source: Table 1.2, p25 of the resubmission.
2L = second line; AE = adverse events; CDK4/6i = cyclin dependent kinase 4/6 inhibitor; ctDNA = circulating tumour DNA; ER = estrogen receptor; *ESR1* = estrogen receptor 1; ET = endocrine therapy; EVE = everolimus; EXE = exemestane; HER2 = human epidermal growth factor 2; HRQoL = health related quality of life; mBC = locally advanced or metastatic breast cancer; OS = overall survival; PFS = progression-free survival; SOC = standard of care.
Note: Elements of the PICO unchanged from the previous submission are highlighted in blue

2 Background

Registration status

2.1 Elacestrant was TGA registered on 11th December 2024 for the treatment of postmenopausal women, and men, with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating *ESR1* variant who have disease progression following at least one line of ET including a CDK 4/6 inhibitor.

Previous PBAC consideration

2.2 A summary of key matters of concern identified by the PBAC in the previous submission is presented in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Comparator	The PBAC considered that in the heavily pre-treated population included in the clinical trial for elacestrant, the control arm of fulvestrant was inappropriate for many patients and was not representative of standard of care. The PBAC considered the outcomes from the pivotal trial are likely to overestimate the clinical benefit for elacestrant due to the inappropriate comparison (para 7.1, elacestrant Public Summary Document [PSD], March 2025 PBAC meeting). The PBAC considered that the treatment algorithm in the 2L setting was complex as there is a range of different treatment options and no clear SOC. There are subgroups of patients for whom a different therapy could be the appropriate comparator depending on the previous treatments or other biomarkers, as well as the line of treatment for elacestrant. The PBAC considered that if the clinical place for elacestrant is in patients naïve to fulvestrant (likely to be endocrine sensitive), and with no visceral crisis, the nominated comparator of ET monotherapy is appropriate. However, for the proposed population, and for patients included in the pivotal trial (EMERALD) ET monotherapy was not representative of SOC as other viable options would be preferred for many patients due to improved efficacy compared with ET monotherapy. (para 7.6, elacestrant PSD, March 2025 PBAC meeting). The PBAC considered a resubmission for elacestrant should provide more clarity regarding the clinical place for elacestrant, and evidence that supports the efficacy over a comparator that reflects standard of care in that patient population (para 7.12, elacestrant PSD, March 2025 PBAC meeting)	Partially addressed. The resubmission nominated EVE + EXE as the main comparator for the proposed drug (elacestrant). The resubmission cited a panel of Australian clinical experts who verified that EVE + EXE was the 2L treatment most likely to be replaced by elacestrant in the target population of patients with an *ESR1* variant and progressive disease after at least 12 month's treatment with ET + CDK4/6i. However, based on a 10% PBS sample analysis presented in the previous submission, only 3% of patients with ER+/HER2- mBC were treated with EVE + EXE after disease progression following CDK4/6i treatment. The ESCs noted that EVE + EXE was nonetheless a reasonable choice of comparator and better represented SoC for the target population than ET.

Component	Matter of concern	How the resubmission addresses it
PBS restriction	The PBAC considered that the clinical criteria in the PBS restriction for elacestrant should specify 'estrogen receptor positive' breast cancer, consistent with the mechanism of action of elacestrant (ER degrader), the TGA indication, and the clinical trial population included in EMERALD. The PBAC also agreed with the ESCs that the requirement for the *ESR1* variant to be an 'activating' variant should be added to the criterion regarding *ESR1* variant status. The PBAC considered that it would be reasonable to exclude the criteria relating to ECOG status to allow clinical judgement regarding patient performance. The PBAC considered it would be reasonable for the restrictions to allow treatment of patients who had received ET + CDK4/6i in the adjuvant setting, as this is consistent with the population in the EMERALD trial and is likely to become increasingly common (para 7.3, elacestrant PSD, March 2025 PBAC meeting).	Addressed. Restriction amended to reflect PBAC comments – see paragraph 3.3.
Economic evaluation – model structure	The model structure did not capture patients at the point of testing as recommended in the PBAC Guidelines (Version 5.0). Although testing costs were included in the model for a single test, costs were underestimated as the proposed restriction allows testing at each episode of disease progression, and no test scenarios were included in the economic model structure (para 7.10, elacestrant PSD, March 2025 PBAC meeting).	Not addressed Although the model has been adapted to allow the user to modify the cost of the test (to investigate scenarios where the cost of the test increases for patients requiring repeated tests), the model initiates with the drug population only (i.e. patients with ER+/HER2- mBC that have received ≥12 months of prior ET + CDK4/6i and who test positive for an activating *ESR1* variant), not the test population as recommended by PBAC guidelines – see paragraph 6.57.
Economic evaluation – truncation point from KM data to extrapolation	The PBAC noted that the submission applied independent parametric extrapolations for OS, PFS, TCD and TTD outcomes. The PBAC considered that the parametric functions for OS and PFS were poorly justified and inappropriately favoured elacestrant. The PBAC noted that the choice of truncation point was not justified as it excluded a large amount of trial data in both treatment arms and favoured elacestrant as the point chosen was where OS curves were most separated (para 7.10, elacestrant PSD, March 2025 PBAC meeting).	Partially addressed Although the resubmission presented an analysis where truncation points were derived using methods from Gebski et al 2018, these were not applied in the base case, with a single truncation point of 28 months used for both PFS and OS in both treatment arms – see 6.61. While the parametric functions were reasonable for PFS (and for OS in the elacestrant arm), the choice of model for OS in the EVE + EXE arm was not the best fit (based on AIC/BIC) – see paragraph 6.62
Economic evaluation – health state utility values	The PBAC noted that the utility value for the PD state was inconsistent with prior submissions and the larger difference between the progression-free and progressed state utility values favoured elacestrant (para 7.10, elacestrant PSD, March 2025 PBAC meeting).	Addressed The current model determined the PD health state utility value by applying the utility decrement for disease progression from Lloyd et al 2006 (-0.272) to the PF utility value reported in EMERALD, consistent with previous submissions considered by the PBAC – see paragraph 6.64.

Component	Matter of concern	How the resubmission addresses it
Utilisation and financial impact	The submission used an epidemiological approach to estimating the use and financial impact of *ESR1* variant testing and elacestrant. The number of incident patients was calculated based on the PBS 10% sample. The PBAC considered that this approach may be reasonable, however the estimated number of prevalent patients was highly uncertain and poorly justified. The PBAC noted that the submission overestimated the *ESR1* variant positive test rate and the PBAC agreed with the ESCs and DUSC that the rate should be no more than 47.7% across multiple lines of treatment, consistent with the EMERALD trial. The PBAC considered that uptake is likely to be overestimated as clinicians would be expected to choose more effective therapies, particularly in more heavily pre-treated patients (para 7.11, elacestrant PSD, March 2025 PBAC meeting).	Addressed The resubmission adopted estimates of incident and prevalent patients from AIHW data (consistent with recent PBAC submissions for mBC) and correctly applied the population prevalence of *ESR1* variants of 47.7% - see paragraph 6.74.

Source: Table 0-1 pp18-21 of the resubmission.
AE = adverse event; CDK4/6i = cyclin dependent kinase 4/6 inhibitor; DUSC= drug utilisation sub-committee; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; ESC = economic sub-committee; ESR1 = estrogen receptor 1; ET = endocrine therapy; EVE = everolimus; EXE = exemestane; ICER = incremental cost-effectiveness ratio; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS =Pharmaceutical Benefits Scheme; PD = progressed disease; PF = progression free; PFS = progression-free survival; PSD = public summary document; SERD = selective estrogen receptor degrader; TCD= time to chemotherapy or death; TGA = Therapeutic Goods Association; TTD = time to treatment discontinuation.

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

3 Requested listing

3.1 The resubmission's revised restriction is outlined below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ELACESTRANT					
elacestrant 345 mg tablet, 28	$[redacted] published price $[redacted] effective price	1	28	5	Orserdu
elacestrant ~~86mg~~ *86.3* mg tablet, 28	$[redacted] published price $[redacted] effective price	2	56	5	Orserdu
elacestrant ~~86mg~~ *86.3* mg tablet, 28	$[redacted] published price $[redacted] effective price	3	84	5	Orserdu

Restriction Summary [new] / Treatment of Concept: [new]		
Concept ID (for internal Dept. use)		**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
		Prescriber type: ☒ Medical Practitioners
		Restriction type: ☒ Authority Required (telephone/online)
Prescribing rule level	7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
	7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
	7608	**Administrative Advice:** Special Pricing Arrangements apply.
	27801	**Administrative Advice:** Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors for the purposes of this restriction are abemaciclib, palbociclib and ribociclib.
	25796	**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.
9818		**Indication:** Locally advanced or metastatic breast cancer
		Treatment Phase: n/a
10659		**Clinical criteria:**
10652		The condition must be estrogen receptor positive
		AND
10660		**Clinical criteria:**
10653		The condition must be human epidermal growth factor receptor 2 (HER2) negative
		AND
New CC1		**Clinical criteria:**
New CC1.1		Patient must have evidence of an activating estrogen receptor 1 (ESR1) variant
		AND
New CC2		**Clinical criteria:**
New CC2.1		Patient must have received at least one prior line of endocrine therapy including at least 12 month's treatment with a CDK4/6 inhibitor prior to initiation of treatment with this drug for this condition
		AND
22195		**Clinical criteria:**
22194		The condition must be inoperable
		AND
		Clinical criteria:
20769		The treatment must be the sole PBS-subsidised therapy for this condition
		AND
		Clinical criteria:
21512		Patient must not have developed disease progression while being treated with this drug for this condition
22201		**Population criteria:**
22200		Patient must not be premenopausal.

New PI	**Prescribing Instructions:** Confirm that the following information is documented/retained in the patient's medical records once only with the first PBS prescription (evidence obtained in relation to past PBS treatment is acceptable): 1) Evidence of HER2 ~~gene amplification~~ *negative status* 2) Evidence of ~~HR status~~ *estrogen receptor positive status* 3) Evidence of an activating ESR1 variant *4) Prior endocrine therapy and CDK4/6 inhibitor (date of commencement and duration of treatment)*

3.2 The resubmission proposed a Special Pricing Arrangement (SPA). The requested effective price was [redacted]% lower than in the previous submission (from $[redacted]/$[redacted] to $[redacted]/$[redacted] [345 mg & 258 mg/172 mg daily dose DPMQ]). The pre-PBAC response proposed a further [redacted]% price reduction in the AEMP from $[redacted] to $[redacted] ($[redacted] DPMQ for the 345 and 258 mg doses).

3.3 Based on PBAC comments from the previous submission, there were several changes to the proposed PBS restriction, including:

- Specifying that the condition must be estrogen receptor positive.
- Specifying that patients must have evidence of an 'activating' ESR1 mutation.
- Excluding criteria relating to ECOG status.

3.4 Additionally, the proposed PBS restriction in the resubmission was updated to specify that patients must have had at least 12 months prior treatment with a CDK4/6i, which the submission noted was used as a marker for sustained endocrine sensitivity and to identify patients likely to receive further clinical benefit from targeted endocrine monotherapies capable of addressing acquired resistance mechanisms, such as activating *ESR1* variants (see paragraph 4.3). The evaluation and the ESCs considered that the changes to the proposed population in the PBS restriction were appropriate and the ESCs considered that the issues previously raised by the PBAC were addressed.

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

4 Population and disease

4.1 In Australia, breast cancer is the second most diagnosed cancer (most common in women) and the fifth most common cause of cancer death (second most common in women), with an estimated 20,336 new cases diagnosed and 3,353 deaths in 2025[1]. Most patients are diagnosed at an early stage; however, patients with advanced disease have substantially poorer survival outcomes (80.6% for Stage III, 32% for Stage IV i.e. mBC).

4.2 ET, with either aromatase inhibitors (AIs) or fulvestrant, plus a CDK4/6i is the recommended Standard of Care (SOC) 1L treatment for patients with ER+/HER2- mBC[2], except for patients with visceral crisis (imminent organ failure) in whom

[1] Cancer Australia. (2025). *Breast cancer in Australia statistics*. https://www.canceraustralia.gov.au/cancer-types/breast-cancer/breast-cancer-australia-statistics

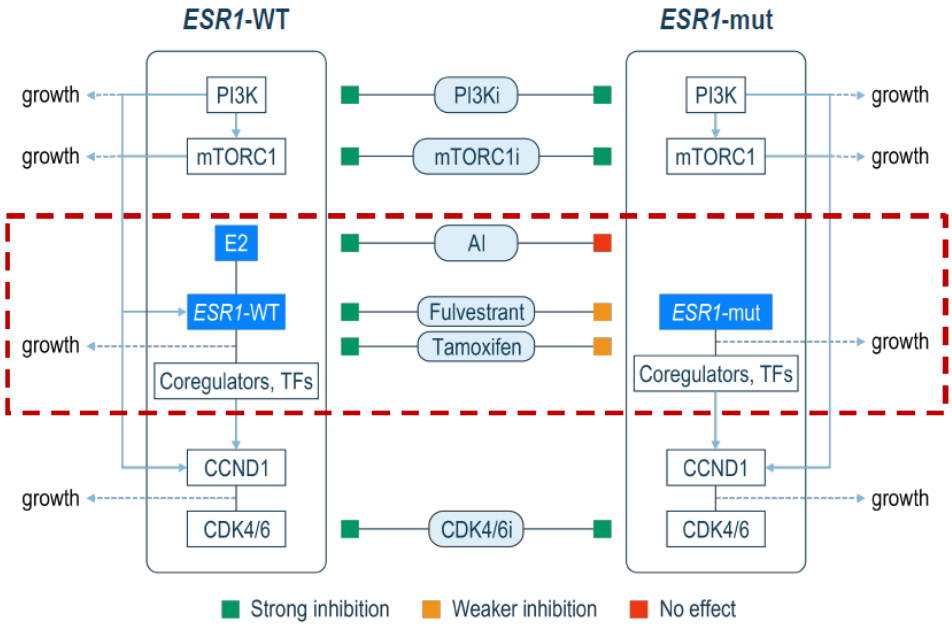
[2] Gennari, A., André, F., Barrios, C. H., et al. (2021). ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Annals of Oncology*, *32*(12), 1475–1495. https://doi.org/10.1016/j.annonc.2021.09.019

chemotherapy is recommended. However, approximately 20% of mBC patients progress rapidly on initial ET (i.e., have de novo or primary resistance, with disease progression within the first 6 months of 1L treatment with ET+ CDK4/6i), while the remaining patients acquire resistance over time (secondary resistance, with disease progression at least 6 months after initiating ET for mBC).

4.3 The resubmission stated that, based on clinical consensus, a threshold of at least 12 months of ET prior to disease progression is used as a surrogate marker for sustained endocrine sensitivity. Patients whose disease progresses after this period are considered more likely to benefit from subsequent targeted ET monotherapies capable of addressing acquired resistance mechanisms, such as activating *ESR1* variants. The additional requirement of at least 12 months of ET prior to disease progression in the proposed treatment population is a key change from the previous submission, which the evaluation and the ESCs considered appropriate. The ESCs considered that this change in the resubmission provided greater clarity regarding the clinical place for elacestrant.

4.4 *ESR1* variants are a key mechanism of acquired resistance to ET. *ESR1* variants are somatic variants that alter the ligand-binding domain (LBD) of estrogen receptors, resulting in a ligand-independent, constitutively active conformation that enhances cancer growth, metastasis, and resistance. This decreases the affinity of estrogen receptors for estrogen (thereby making AIs, which reduce estrogen production, ineffective), selective estrogen receptor modulators (SERMs- eg tamoxifen) and selective estrogen receptor degraders (SERDs – eg fulvestrant) (See Figure 1).

Figure 1: Mechanisms of resistance in ER+/HER2- mBC



Source: Figure 1.3, p26 of the previous submission.

AI = aromatase inhibitor; CCND1 = cyclin D1; CDK4/6 = cyclin-dependent kinase 4 and 6; ER+/ HR2-mBC = estrogen receptor positive, human epidermal growth factor receptor 2 metastatic breast cancer; *ESR1-WT* = estrogen receptor 1 wild type; *ESR1*-mut = estrogen receptor 1 variant; E2 = estradiol; mTORC = mammalian target of rapamycin complex; PI3K = phosphoinositol three kinase; TFs = transcription factors;
Note: In the *ESR1*-WT situation, AI depletion of estrogen inhibits *ESR1* activity, SERMs such as tamoxifen alter *ESR1* binding partners and transactivation ability, and SERDs such as fulvestrant inhibit *ESR1* activity and proteolytic stability. In the *ESR1*-mut situation, AI is ineffective since *ESR1*-mut does not require estrogen, and tamoxifen and fulvestrant bind less strongly to *ESR1*-mut. CDK4/6i is effective in both *ESR1*-wt and *ESR1*-mut BC.

4.5 *ESR1* variants are rarely detected in treatment-naive primary tumours[3], occurring more frequently with longer exposure to conventional ET, particularly AIs[4]. The duration of exposure to ET in 1L treatment has increased due to combination with CDK4/6i, with median PFS typically ranging from between 20 to 28 months[5]. As such, *ESR1* variants predominantly emerge during 1L treatment, although they may develop during any subsequent line of therapy; therefore, testing for *ESR1* variants is relevant at each episode of disease progression. It is estimated that up to 50% of patients with ER+/HER2- mBC will develop *ESR1* variants during their treatment course, the majority of which will arise following disease progression on 1L therapy[4].

4.6 Patients harbouring *ESR1* variants have a poorer prognosis, with inferior PFS and OS outcomes[6], as currently available 2L+ treatments are less effective (tamoxifen, fulvestrant) or not effective (in the case of AIs). Chemotherapy is an alternative treatment option for these patients but is associated with toxicities, which impact HRQoL.

4.7 Elacestrant is a potent, selective, and orally active ERα antagonist and SERD. Elacestrant inhibits the estrogen-dependent and independent growth of ERα-positive breast cancer cells, including those harbouring *ESR1* gene variants, thus providing a 2L+ treatment option for patients with ER+/HER2-mBC and *ESR1* variants.

4.8 Recent updates to European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines have added elacestrant as a recommended treatment option for postmenopausal females and adult males with ER+/HER2- mBC who test positive for *ESR1* variants after disease progression following at least one line of ET including a CDK4/6i.

4.9 The proposed Australian clinical management algorithm with the introduction of the codependent technologies is presented in Figure 2. The ESCs noted that the use of elacestrant in the proposed treatment algorithm is in line with NCCN guidelines.

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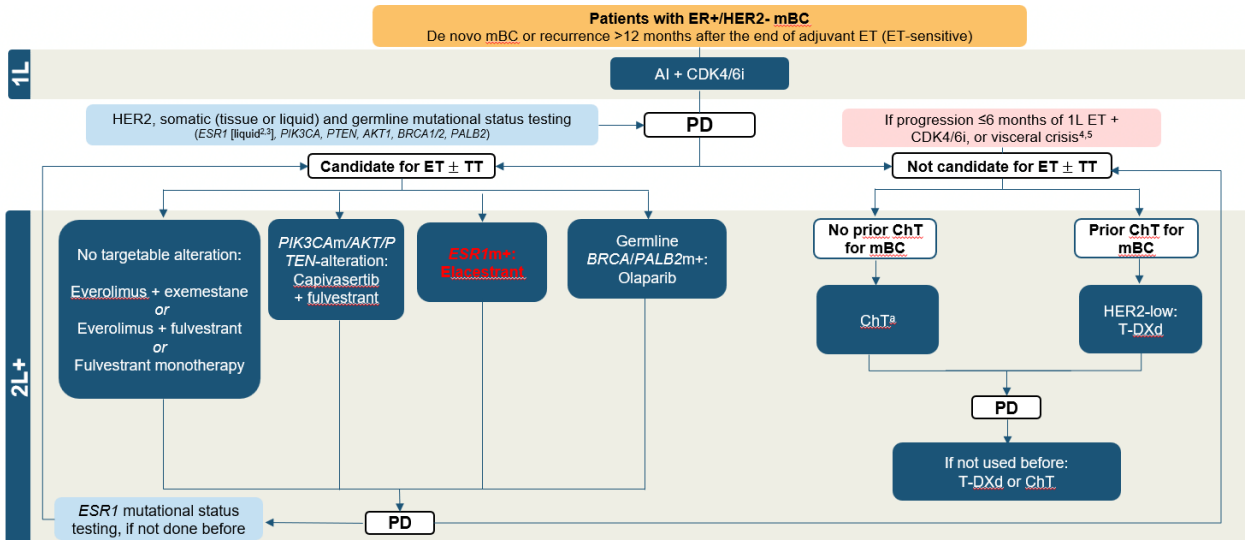
[3] Hartkopf, A. D., Grischke, E., & Brucker, S. Y. (2020). Endocrine-Resistant Breast Cancer: Mechanisms and Treatment. *Breast Care (Basel)*, 15(4):347-354.

[4] Brett, J. O., Spring, L. M., Bardia, A., & Wander, S. A. (2021). *ESR1* mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res*, 23(1):85.

[5] Piezzo, M. C. (2020). Progression-Free Survival and Overall Survival of CDK 4/6 Inhibitors Plus Endocrine Therapy in Metastatic Breast Cancer: A Systematic Review and Meta-Analysis. . *International Journal of Molecular Science*, 21(17) 6400.

[6] Turner, N. C., Swift, C., Kilburn, L., Fribbens, C., Beaney, M., & et al. (2020). *ESR1* Mutations and Overall Survival on Fulvestrant versus Exemestane in Advanced Hormone Receptor-Positive Breast Cancer: A Combined Analysis of the Phase III SoFEA and EFECT Trials. Clin Cancer Res, 26(19):5172-5177.

Figure 2 : Proposed Australian treatment algorithm to include *ESR1* variant testing and treatment with elacestrant



Source: Figure 1.4, p39 of the resubmission

1/2L = first/second line; AI = aromatase inhibitor; *BRCA* = BReast CAncer gene; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ChT = chemotherapy; ER = estrogen receptor; *ESR1* = estrogen receptor 1 gene; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; mBC = locally advanced or metastatic breast cancer; PALB2 = partner and localizer of *BRCA2*; PD = progressive disease; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase; T-DXd = trastuzumab deruxtecan.

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

5 Comparator

5.1 In the previous submission, no testing for *ESR1* variants and ET monotherapy (fulvestrant or an AI) were nominated as the codependent comparators. The choice of ET monotherapy aligned with the comparator arm of EMERALD, where 73% of patients received fulvestrant and 27% of patients received an AI (para 5.1, elacestrant PSD, March 2025 PBAC).

5.2 The PBAC previously considered that the treatment algorithm in the 2L setting was complex as there is a range of different treatment options and no clear SOC. There are subgroups of patients for whom a different therapy could be the appropriate comparator depending on the previous treatments or other biomarkers, as well as the line of treatment for elacestrant. The PBAC considered that if the clinical place for elacestrant is in patients naïve to fulvestrant (likely to be endocrine sensitive), and with no visceral crisis, the nominated comparator of ET monotherapy is appropriate. However, for the proposed population, and for patients included in the pivotal trial (EMERALD) ET monotherapy was not representative of SOC as other viable options would be preferred for many patients due to improved efficacy compared with ET monotherapy (para 7.6, elacestrant PSD, March 2025 PBAC).

5.3 The PBAC previously considered a resubmission for elacestrant should provide more clarity regarding the clinical place for elacestrant, and evidence that supports the efficacy over a comparator that reflects SOC in that patient population (para 7.12, elacestrant PSD, March 2025 PBAC).

5.4 The resubmission nominated no testing for *ESR1* variants and everolimus plus exemestane (EVE + EXE) as the codependent comparators. EVE + EXE was chosen to

represent SOC second line (2L treatment) in the target population of patients with progressive disease after at least 12 month's treatment with ET + CDK4/6i. This was based on a panel of Australian clinical experts who verified that EVE + EXE was the 2L treatment most likely to be replaced by elacestrant.

5.5 The resubmission acknowledged the recent PBS listing of capivasertib plus fulvestrant (CAPI + FULV) combination therapy, for the ER+/HER- mBC population with confirmed AKT pathway alterations (PIK3CA/AKT1/PTEN). The Sponsor stated there is no reasonable basis that CAPI + FULV will be used interchangeably in clinical practice in patients with an identified ESR1 variant, therefore CAPI+FULV was not considered a comparator in this resubmission. However, the evaluation considered that if patients were to have both *ESR1* variants and AKT pathway alterations, CAPI + FULV would be a relevant comparator. The ESCs estimated that 10-26% of patients may have both *ESR1* variants and AKT pathway alterations, however it is likely that they would use CAPI + FULV and elacestrant sequentially.

5.6 The resubmission also identified active TGA applications for imlunestrant + abemaciclib and camizestrant + CDK4/6i:

- Imlunestrant tosylate for "the treatment of adults with a specific type of breast cancer that has spread to other parts of the body and that was previously treated with hormone therapy" (April 2025). The Sponsor assumed that this application was based on the EMBER-3 trial (Jhaveri et al., 2023), which assessed the 2L treatment of mBC with either imlunestrant, SOC ET (exemestane or fulvestrant), or combination imlunestrant + abemaciclib. Imlunestrant was not considered to be a near market comparator in the resubmission, however, no reasoning/justification was provided.
- Camizestrant (in combination with a CDK4/6i) for "the treatment of adult patients with HR-positive, HER2-negative, mBC upon detection of *ESR1* variant during first line endocrine-based therapy" (July 2025). MSAC application 1816 for "*ESR1* variant testing to determine the eligibility for treatment with camizestrant" was considered by PASC in April 2026; however, the intention of treatment with camizestrant is to substitute for the AI component of 1L combination treatment upon the detection of a developing *ESR1* variant, before radiological disease progression. As such, camizestrant was not considered to be a near market comparator in the resubmission, which the evaluation and the ESCs considered appropriate

5.7 The previous submission presented results from a 2023 10% PBS sample analysis of subsequent therapies following disease progression after CDK4/6i treatment in patients with ER+/HER2- mBC. The most common subsequent therapy was AI monotherapy (37%), no further treatment (21% - patients likely to move to clinical trials or access programs), no hormonal treatment (17% - taken to be chemotherapy regimens) and fulvestrant monotherapy (14%). Only 3% of patients received EVE + EXE.

5.8 Additionally, the PBAC previously noted that the pre-PBAC response argued that everolimus is rarely used in Australia due to toxicity (para 5.5, elacestrant PSD, March 2025 PBAC).

5.9 The evaluation and the ESCs considered that the heterogenous nature of current 2L treatments for ER+/HER2- mBC following disease progression after treatment with a CDK4/6i makes the selection of a treatment comparator challenging (see para 4.9). The ESCs considered that in the absence of testing for *ESR1* variants among the target population of patients with endocrine sensitivity (≥12 months 1L treatment with CDK4/6i + AI), EVE + EXE, everolimus + fulvestrant (EVE + FULV), fulvestrant monotherapy, or cytotoxic chemotherapy are relevant 2L treatment options. The evaluation and the ESCs considered that the choice of EVE + EXE as the main comparator in the resubmission was not well justified, noting the small number of ER+/HER2- mBC patients using EVE + EXE in Australia and previous concerns over toxicity. The Pre-Sub-Committee Response (PSCR) agreed that the selection of a treatment comparator is difficult, reiterating that the choice of comparator for the resubmission (EVE + EXE) was informed with the assistance of a panel of Australian expert physicians, and remains the most pragmatic approach. However, the PSCR did not address the results from the 2023 10% PBS sample analysis, discussed in paragraph 5.7. The ESCs considered that EVE + EXE was a reasonable comparator for the ET sensitive population and that it would reflect standard of care better than ET monotherapy as it is a more active/intense treatment. The ESCs considered that chemotherapy (eg capecitabine) remains a reasonable comparator for some patients, but noted that no comparison with chemotherapy was presented.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician advised that there was strong clinical interest in SERDs such as elacestrant and camizestrant as biomarker-driven treatments and that these treatments appear to be well tolerated. The clinician advised that elacestrant would be used for patients who have had good outcomes with CDK4/6i + AI treatment but have subsequently had disease progression to lymph nodes or progression within the bone. The clinician advised that most patients who receive CDK4/6i would meet the eligibility criteria related to CDK4/6i use as the trial data reported many patients can have two years of PFS on CDK4/6i. The clinician advised that elacestrant is likely to be used in patients who have a strong preference to avoid or delay the need for chemotherapy where possible and avoid treatments that require frequent clinic visits.

6.2 The clinician advised that EVE + EXE was a reasonable comparator and its low use in the PBS data may be due to patients having previously used exemestane and having experienced disease progression. The clinician advised that capivasertib is a possible alternative treatment however biomarker testing is not always available or timely and there are concerns related to adverse events. The clinician advised that there is also

some use of fulvestrant in patients with a good response to CDK4/6i, who have a good performance status, and do not wish to use capivasertib, though the PFS benefit is small.

6.3 The PBAC considered that the hearing was informative as it provided a clinical perspective on how treatments are selected for patients who have progressed following CDK4/6i +AI therapy.

Consumer inputs

6.4 The PBAC noted and welcomed the input from health care professionals (1) and organisations (5) via the Office of Health Technology Assessment Consultation Hub. The inputs described a range of benefits of treatment with elacestrant including improved disease control, increased treatment choice, more manageable side-effects for some patients, and the convenience of an oral therapy. The health professional noted there are currently no treatments specifically targeting acquired *ESR1* mutations, and considered elacestrant a reasonably effective and well-tolerated option for the right patients. The health professional stated treatment should be used within sensible clinical guardrails, noting that access to elacestrant via PBS-listing would support alignment with international guidelines and comparable healthcare systems. The healthcare professional considered elacestrant should not be used later in lines where it may be less effective.

6.5 Consumer organisations (Breast Cancer Network Australia, MBC Action Australia, Rare Cancers Australia and So Brave) emphasised the high unmet need for treatments following progression on endocrine therapy plus CDK4/6i, the value of additional progression-free survival, and the importance of access to both *ESR1* testing and a targeted therapy to avoid use in patients where treatment would be ineffective. The input also highlighted improvements in quality of life associated with an oral option and that fulvestrant injections are painful for patients.

6.6 The PBAC noted that the consumer inputs received for the March 2025 submission discussed similar issues.

6.7 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the elacestrant submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the EMERALD trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale version (ESMO-MCBS) for elacestrant, which was 3 (out of a maximum of 5, where 5 and 4 in the non-curative setting represent the grades with substantial improvement)[7], based on a comparison with ET from the EMERALD trial.

[7] Cherny NI, et al. ESMO-magnitude of clinical benefit scale version 2.0 (ESMO-MCBS v2. 0). Annals of Oncology. 2025 Aug 1;36(8):866-908.

Overview of the evidence base

6.8 The approach taken for the linked evidence component of the co-dependency was unchanged for the resubmission.

6.9 Compared to the previous submission the resubmission presented different direct test-to-health outcomes evidence, due to the change in selected comparator. Only indirect evidence was available for the resubmission's selected comparator.

6.10 The use of the *post hoc* defined subgroup of EMERALD patients in the resubmission (Table 3) is discussed further below (paragraphs 6.13, 6.14). The resubmission ITC used only biomarker positive (*ESR1* variant) evidence (see paragraph 6.33).

Table 3: Direct evidence provided in the resubmission to support the codependent technology

Study design	Extent of evidence supplied	Overall risk of bias in clinical trials
Post hoc identified subgroup of EMERALD (biomarker positive only)	☒ k=1 n=78	High

Source: Bardia et al, 2024.
k=number of studies; n=overall number of patients

Clinical trials on the safety/effectiveness of elacestrant

6.11 The EMERALD trial (Bidard et al, 2022; Bardia et al, 2024) comprised the only direct evidence presented in the resubmission (of elacestrant vs SOC [as monotherapy with either fulvestrant or an AI]); however the comparator does not align with the resubmission's nominated comparator (EVE + EXE). No updated trial data or final clinical study report (CSR) for EMERALD was included, although a final CSR would have been expected based on trial timelines. The resubmission relied on a subgroup identified using a *post hoc* analysis of the EMERALD data (Bardia et al, 2024), described below (paragraph 6.13).

6.12 The key reports and trial publications of the resubmission are listed in Table 4 for the direct evidence and a summary of the key features in Table 5.

Table 4: Summary of the direct evidence used in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials: elacestrant vs SOC (as monotherapy with fulvestrant or AI)		
EMERALD NCT03778931	**Clinical study reports:** RAD1901-308 Elacestrant Monotherapy vs Standard of Care for the Treatment of Patients with ER+/HER2- Advanced Breast Cancer Following CDK4/6 Inhibitor Therapy: A Phase 3 Randomised, Open-Label, Active-Controlled, Multicenter Trial. Clinical Study Report v.2 (6 January 2023) RAD1901-308 Elacestrant Monotherapy Vs. Standard Of Care For The Treatment Of Patients With ER+/HER2- Advanced Breast Cancer Following CDK4/6 Inhibitor Therapy: A Phase 3 Randomised, Open-Label, Active-Controlled, Multicenter Trial (EMERALD). Overall Survival Addendum to Clinical Study Report v.2.	Interim CSR (primary analysis for PFS) (6 September 2021 data cutoff) CSR OS Addendum (data cutoff 2 September 2022)
	Key peer-reviewed publications: Bidard et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. **Additional peer-reviewed publications:** Bardia et al. Elacestrant in ER+, HER2- Metastatic Breast Cancer with ESR1-Mutated Tumors: Subgroup Analyses from the Phase III EMERALD Trial by Prior Duration of Endocrine Therapy plus CDK4/6 Inhibitor and in Clinical Subgroups.	J Clin Oncol. 2022 Oct 1;40(28):3246-3256. Clin Cancer Res. 2024 Oct 1;30(19):4299-4309.

Source: Table 2.4: Randomised controlled trials (and associated reports) identified for Elacestrant, pp55 – 56 of the resubmission
AI = aromatase inhibitor; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CSR = clinical study report; ER+/HR2- = estrogen receptor-positive, HER2-negative; *ESR1* = estrogen receptor 1; mBC = metastatic breast cancer; PFS = progression free survival; SOC = standard of care.
Note: Key reports and publications used in the evaluation only. Information included in the previous submission is shaded blue.

Table 5: Key features of the included direct evidence

Trial	N	Design/ duration	Patient population	Outcome(s)	Used in model
Elacestrant vs SOC (monotherapy with fulvestrant or AI. in both *ESR1* variant positive and negative patients)					
Bidard 2022	478	R, DB, MC median duration follow-up 15.9 months for PFS (26.0 months for OS)	ER+/HER2- mBC with disease progression following at least one line of ET, including a CDK4/6i	PFS, OS	PFS, OS

Source: Compiled during the evaluation using information from the EMERALD CSR and CSR addendum.
CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; DB = double blind; ER+/HER2-mBC = estrogen receptor positive/ human epidermal growth factor receptor 2 negative metastatic breast cancer; ESR1 = estrogen receptor 1; ET = endocrine therapy; MC = multi-centre; OS = overall survival; PFS = progression-free survival; R = randomised; SOC = standard of care.
Outcomes excluded from this table for evaluation of the resubmission: clinical benefit rate (CBR); duration of response (DoR); objective response rate (ORR); time to chemotherapy or death (TCD), time to treatment discontinuation (TTD).
Information included in the previous submission is shaded blue.

6.13 The *post hoc* defined subgroup of the EMERALD participants (who were *ESR1* variant positive, and had received at least 12 months prior treatment with ET and a CDK4/6 inhibitor) formed the elacestrant arm for the resubmission ITC. The evaluation considered the outcomes reported for the *post hoc* subgroup used in the ITC were at high risk of bias as it could not be determined whether the patients were selected objectively (such as whether these were chosen by independent clinicians blinded to treatment allocation and trial outcomes). Other sources of bias and type I error due to multiple analyses could not be ruled out.

6.14 The choice of the ≥12 months prior treatment subgroup was based on an analysis reported briefly in Bardia et al, (2024) which compared outcomes for EMERALD participants meeting the 12 months prior treatment criterion versus those who received less than 12 months prior ET + CDK4/6 inhibitor treatment. A test for interaction between these two groups was statistically significant (P=0.014), however the resubmission did not provide details of the Bardia et al (2024) analysis for review.

6.15 The resubmission identified several potential sources of indirect evidence for the comparator EVE + EXE including three randomised controlled trials (RCTs) BOLERO-2 (Baselga et al, 2012), BOLERO-6 (Jerusalem et al, 2018), evERA (Mayer et al, 2025) and one analysis of a US cancer centre patient health record database (Flatiron Health, 2024). The resubmission's literature search for indirect evidence of trials for comparators representing current SOC (including EVE + EXE) was limited to RCTs, and information was missing regarding selection of the included data sources. The resubmission's indirect treatment comparison (ITC) drew on non-RCT evidence (Flatiron Health 2024), therefore an additional literature search should have been presented describing the process for selecting the Flatiron data and describing potential sources of non-RCT clinical data for EVE + EXE. Overall, the evaluation considered that the literature search presented in the resubmission was not adequate.

6.16 The PSCR stated that the criteria for selection of non-RCT data sources used in the ITC required: (1) detailed documentation of activating ESR1 variants, (2) sufficient sample size and data quality, (3) regulatory/HTA acceptability. The PSCR stated that selection of the clinico-genomic database from Flatiron Health was based on its comprehensive and well-accepted data at a time where information on *ESR1* mutation testing and related mutations were still very rarely captured. The ESCs noted that alternative data sources had smaller sample sizes (Patient360 Breast database) or had limited published data available (evERA trial).

6.17 The key reports and trial publications of the resubmission are listed in Table 6 for the indirect evidence. The key features of indirect evidence used in the ITC are in Table 7. The ITC was an unanchored matching adjusted indirect comparison (MAIC) as there was no common comparator – the EVE + EXE arm constructed from the Flatiron Health data was single arm (N=32).

Table 6: Summary of the indirect evidence used in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Indirect evidence: EVE + EXE comparator RCTs (safety only)		
BOLERO-2 NCT00863655	**Key peer-reviewed publications:** Baselga J, Campone M, Piccart M, Burris III HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. Yardley DA, Noguchi S, Pritchard KI, Burris III HA, Baselga J, Gnant M, Hortobagyi GN, Campone M, Pistilli B, Piccart M, Melichar B. Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression-free survival analysis. Chandarlapaty S, Chen D, He W, Sung P, Samoila A, You D, Bhatt T, Patel P, Voi M, Gnant M, Hortobagyi G, Baselga J, Moynahan ME. Prevalence of ESR1 Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial.	New England Journal of Medicine. 2012 Feb 9;366(6):520-9. Advances in Therapy. 2013 Oct;30(10):870-84. JAMA Oncol. 2016 Oct 1;2(10):1310-1315.
BOLERO-6 NCT01783444	**Peer-reviewed publications:** Jerusalem G, de Boer RH, Hurvitz S, Yardley DA, Kovalenko E, Ejlertsen B, Blau S, Özgüroglu M, Landherr L, Ewertz M, Taran T, Fan J, Noel-Baron F, Louveau AL, Burris H. Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer: The BOLERO-6 Randomized Clinical Trial.	JAMA Oncol. 2018 Oct 1;4(10):1367-1374.
Indirect evidence: EVE + ET comparator RCT		
evERA trial NCT05306340	**Conference abstracts:** Mayer E, Tolaney S, Martin M, Vidal G, Moscetti L, Jhaveri K, Brufsky A, Gradishar W, Schneeweiss A, Niikura N, Favret A. LBA16 Giredestrant (GIRE), an oral selective estrogen receptor (ER) antagonist and degrader,+ everolimus (E) in patients (pts) with ER-positive, HER2-negative advanced breast cancer (ER+, HER2–aBC) previously treated with a CDK4/6 inhibitor (i): Primary results of the phase III evERA BC trial. ESMO Congress, Berlin Germany, 17-21 October 2025.	Annals of Oncology. 2025 Sep 1;36:S1676-7.
Indirect evidence: EVE + EXE patient health record data (Flatiron database)		
Flatiron Health (2024) report	**Internal report:** FINAL STUDY REPORT. Real-world PFS and OS among patients with ESR1+, ER+/HER2-, advanced/metastatic breast cancer treated with everolimus and exemestane combination therapy post-CDK4/6 inhibitor. Sponsor: Stemline Therapeutics Switzerland GmbH. April 5, 2024.	Attachment 1.1.3 - Final Flatiron Report_mBC_Eve_Exe_V2_4.5.24

Source: Table 2.4: Randomised controlled trials (and associated reports) identified for Elacestrant, pp55–56 of the resubmission; Table 2.5: Trials and associated reports identified for EVE+EXE, pp56-57 of the resubmission.

CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CSR = clinical study report; ER+ = estrogen receptor-positive; ESR1 = estrogen receptor 1 gene; EVE + EXE = everolimus + exemestane; HR2- = HER2-negative; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; mBC = metastatic breast cancer; PFS = progression free survival.

Note: Key reports and publications used in the evaluation only. Conference abstracts were not included for the indirect evidence unless data unavailable from the peer-reviewed literature were presented in the resubmission.

Table 7: Key features of the evidence used in the indirect comparison

Trial	N	Design	Patient population	Outcomes	Used in model
Indirect evidence: Elacestrant (in *ESR1* variant positive patients) (non-comparative)					
Bardia et al, 2024	78	*Post hoc* identified subgroup of EMERALD	EMERALD participants with *ESR1* variant, and at least 12 mo of prior ET+CDK4/6i	PFS, OS	PFS, OS
Indirect evidence: EVE + EXE (in *ESR1* variant positive patients) (non-comparative)					
Flatiron Health (2024) report	32	Retrospective analysis of a patient health record database	Flatiron participants, aged ≥50y, ESR1 variant positive, with at least 12 mo of prior ET+CDK4/6i	rwPFS, rwOS	rwPFS, rwOS
Mayer et al, (2025)	105	Stratified evERA subgroup	*ESR1* variant, prior CDK4/6i Tx in adjuvant or advanced/ metastatic setting, receiving ET[a]+everolimus in 1st, 2nd, or 3rd line.	PFS	PFS

Source: compiled during the evaluation from: Section 2B.6.1.1. Elacestrant: ESR1 mutation and ≥12 months prior treatment with an ET + CDK4/6i (post hoc subgroup analyses) (resubmission pp108-110); Section 2B.4.2. Flatiron real world retrospective cohort study (Flatiron Health 2024) (resubmission pp78-81).

CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ER+ = estrogen receptor-positive; ESR1 = estrogen receptor 1 gene; EVE + EXE = everolimus + exemestane; HR2- = HER2-negative; OS = overall survival; PFS = progression free survival; rwOS = real world overall survival; rwPFS real world progression-free survival; Tx = treatment; y = years.

a ET for use in combination with everolimus in the evERA trial (Mayer et al, 2025) was defined as physician's choice of exemestane, fulvestrant or tamoxifen.

Note: Although the EMERALD N=78 post hoc identified subgroup was included in the previous submission it was not used as the basis of comparative efficacy claims as is the case for the resubmission and has not been shaded blue.

6.18 The indirect evidence presented for the EVE + EXE arm of the ITC was sparse. The BOLERO-2 and BOLERO-6 trials were presented in the resubmission for a naïve comparison of safety only and did not form the basis of support for comparative efficacy. Further comments on the BOLERO trials are below (paragraph 6.44 to 6.45).

6.19 The evERA study publication (Mayer et al, 2025) was a conference abstract with very limited trial information or clinical results, and was presented for a supplementary ITC only. The evERA trial compared giredestrant + EVE versus EVE + ET (physician's choice of exemestane, fulvestrant or tamoxifen) in patients who had progressed on prior CDK4/6 inhibitors and were stratified by *ESR1* variant status. The resubmission presented a supportive ITC using the EVE + ET arm from evERA as the comparator in a supportive ITC. The evaluation and the ESCs considered that the evERA trial ITT population may not adequately represent the line of therapy sought or the chosen comparator in the resubmission. The evaluation considered that a more complete trial publication including subgroup data may address some of these issues.

6.20 The Flatiron Health (2024) data used in the ITC were retrospective, observational, single arm, comprised small numbers of patients (N=32) and represented a low level of evidence. No information was provided to confirm data were selected objectively, without selection bias.

6.21 The ITC compared elacestrant versus EVE + EXE in *ESR1* variant positive patients. The absence of data for patients without an *ESR1* variant in the evidence used for the ITC limited the conclusions that could be drawn for predictive validity of the *ESR1* biomarker (*see Claim of codependence*).

Comparative effectiveness

Evidence presented for the claim of codependence: EMERALD

6.22 A summary of the PFS and OS results from EMERALD comparing the whole trial population and those with and without the *ESR1* variant is presented in Table 8. Also included are results from the *post hoc* defined subgroup (*ESR1* variant only; ≥12 months prior ET+CDK4/6i treatment) on which the resubmission relied for the elacestrant arm in the ITC. The PSCR provided biomarker negative (*ESR1* non-variant) results and the test for interaction for the post hoc CDK4/6i ≥ 12 months subgroup analysis.

Table 8: EMERALD: PFS & OS in whole trial, *ESR1* variant, *ESR1* non-variant and post hoc subgroups (ITT)

Population	Elacestrant		SOC [a]		HR (95% CI); p-value
	Event n/N (%)	Median, months (95%CI)	Event n/N (%)	Median, months (95%CI)	
PFS (prespecified analysis) (September 2021 data cut off)					
Whole trial population	144/239 (60.3)	2.79 (1.94, 3.78)	156/239 (65.3)	1.91 (1.87, 2.10)	**0.70 (0.55, 0.88); 0.0018**
ESR1 variant	62/115 (53.9)	3.78 (2.17, 7.26)	78/113 (69.0)	1.87 (1.87, 2.14)	**0.55 (0.39, 0.77); 0.0005**
ESR1 non-variant	82/124 (66.1)	1.94 (1.87, 3.55)	78/126 (61.9)	1.97 (1.87, 2.20)	0.86 (0.63, 1.19); 0.31
Test for interaction – ESR1 variant status [b]					0.053
mPFS by BIRC CDK4/6i ≥ 12 months subgroup (September 2022 data cut off)					
ESR1 variant	39/78 (50.0)	8.61 (4.14, 10.84)	52/81 (64.2)	1.91 (1.87, 3.68)	0.410 (0.262, 0.634)
ESR1 non-variant	49/72 (68.1)	2.33 (1.87, 3.68)	48/78 (61.5)	2.04 (1.87, 3.68)	0.897 (0.592, 1.356)
Test for interaction – ESR1 variant status in population ≥12 months of prior CDK4/6i [d]					0.0092
OS (September 2022 data cut off)					
Whole trial population	124/239 (51.9)	24.61 (20.67, 29.47)	121/239 (50.6)	22.57 (18.14, 28.88)	0.91 (0.71, 1.18); 0.48
ESR1 variant	61/115 (53.0)	24.18 (20.53, 28.71)	60/113 (53.1)	23.49 (15.64, 29.90)	0.90 (0.623, 1.30); 0.58
ESR1 non-variant	63/124 (50.8)	26.12 (18.83, NC)	61/126 (48.4)	22.57 (18.37, 30.98)	0.92 (0.65, 1.31); 0.65
Test for interaction – *ESR1* variant status [b]					0.93

Source: compiled from:
Table 2.17: Key PFS and OS results from the EMERALD trial (ITT analysis), p86 of the resubmission.
Table 2.35: Blinded IRC-assessed PFS - All patients with ESR1 mutation who had received ≥12 months of prior ET + CDK4/6i - DCO 2nd September 2022, resubmission p109.
ESR1-Mutated Breast Cancer: Survival Analysis by CDK4/6 Inhibitor Duration (8 April 2026) – received during evaluation.
CI = confidence interval; CDK4/6i = cyclin dependent kinase type 4/6 inhibitor; ESR1 = estrogen receptor 1; ESR1-mut = ESR1 mutated; ESR1-mut-nd = ESR1 variant not detected; ET = endocrine therapy; HR = hazard ratio; ITT = intent to treat analysis population; mPFS = metastatic progression free survival; mo = month; NC = not calculable; NR = not reported; OS = overall survival; PFS = progression-free survival; SOC = standard of care.
[a] SOC in the EMERALD trial comprises of choice of aromatase inhibitor (AI) or fulvestrant monotherapy.
[d] Test for interaction comparing the subgroups with either ≥12 months or ≤12 months prior treatment with a CDK4/6 inhibitor. A p value <0.05 would be considered statistically significant and suggest that ≥12 months prior treatment was a potential treatment effect modifier.
Note: p-values using stratified log-rank test.
Bold text indicates a statistically significant p-value
Information included in the previous submission is shaded blue. Although PFS for the EMERALD N=78 post hoc identified subgroup was included in the previous submission it was not used as the basis of comparative efficacy claims as is the case for the resubmission.

6.23 Data for the EMERALD trial overall were unchanged for the resubmission, including the prespecified *ESR1* variant subgroup (Table 8). Key findings from the EMERALD trial were: the HR for progression with elacestrant versus AI/FULV monotherapy was statistically significant in the whole trial population (HR 0.70 [95% CI 0.55, 0.88],

p=0.0018) and in the *ESR1* variant subgroup (HR 0.55 [95% CI 0.39, 0.77], p=0.0005). In the *ESR1* variant patients, the difference in median PFS was 1.91 months (elacestrant vs SOC). In considering the previous submission, the PBAC stated that this PFS improvement was modest (paragraph 7.8, elacestrant PSD March 2025 PBAC meeting).

6.24 PFS by BIRC in the *ESR1* non-variant subgroup was not statistically significant for elacestrant versus SOC (HR 0.86 [95% CI 0.63, 1.19] p=0.31). The PBAC previously considered that there appeared to be minimal benefit in the non-*ESR1* subgroup (paragraph 7.4, elacestrant PSD March 2025 PBAC meeting).

6.25 A test of interaction between the two prespecified EMERALD subgroups (*ESR1* variant vs *ESR1* non-variant) was not statistically significant (p=0.053) (Bardia et al, 2024) suggesting *ESR1* had limited predictive validity for elacestrant benefit. The PBAC previously noted the ESC rationale that although the test for interaction did not reach statistical significance there appeared to be minimal benefit in the non-*ESR1* subgroup and the clinical rationale and mechanism of action for elacestrant supported the claim that *ESR1* is likely to be a predictive biomarker for treatment with elacestrant. The ESCs previously considered the claim of codependence to be reasonable overall, but the extent of treatment effect variation to be uncertain (paragraph 6.32, elacestrant PSD, March 2025 PBAC meeting).

6.26 The ESCs noted that the claim of codependence was not previously considered by PBAC to be key issue in the original submission.

Elacestrant Arm (Post hoc defined EMERALD subgroup)

6.27 The Table below presents the PFS and OS data for the whole trial population and in the CDK4/6i ≥ 12 months post hoc subgroup as relied on in the resubmission.

Table 9: EMERALD: PFS & OS in whole trial, post hoc subgroups (ITT)

Population	Elacestrant		SOC [a]		HR (95% CI); p-value
	Event n/N (%)	Median, months (95%CI)	Event n/N (%)	Median, months (95%CI)	
PFS (prespecified analysis) (September 2021 data cut off)					
Whole trial population	144/239 (60.3)	2.79 (1.94, 3.78)	156/239 (65.3)	1.91 (1.87, 2.10)	**0.70 (0.55, 0.88); 0.0018**
PFS (*post hoc* analysis) (September 2022 data cut off)					
Post hoc subgroup *ESR1* variant; ≥12 mo prior ET+CDK4/6i [c]	39/78 (50)	8.61 (4.14 to 10.84)	53/81 (65.4)	1.91 (1.87 to 3.68)	**0.410 (0.262, 0.634) <0.0001**
Post hoc subgroup *ESR1* variant; ≤12 mo prior ET+CDK4/6i [c]	NR	NR	NR	NR	1.10 (0.59, 2.06); 0.7721
Test for interaction – ≥12 months of prior CDK4/6i [d]					**0.014**
OS (September 2022 data cut off)					
Whole trial population	124/239 (51.9)	24.61 (20.67, 29.47)	121/239 (50.6)	22.57 (18.14, 28.88)	0.91 (0.71, 1.18); 0.48
Post hoc subgroup *ESR1* variant; ≥12 mo prior ET+CDK4/6i [c]	38/78 (48.7)	27.73 (21.49, 31.93)	38/81 (46.9)	27.66 (16.95, 32.62)	0.856 (0.541, 1.353) 0.5043

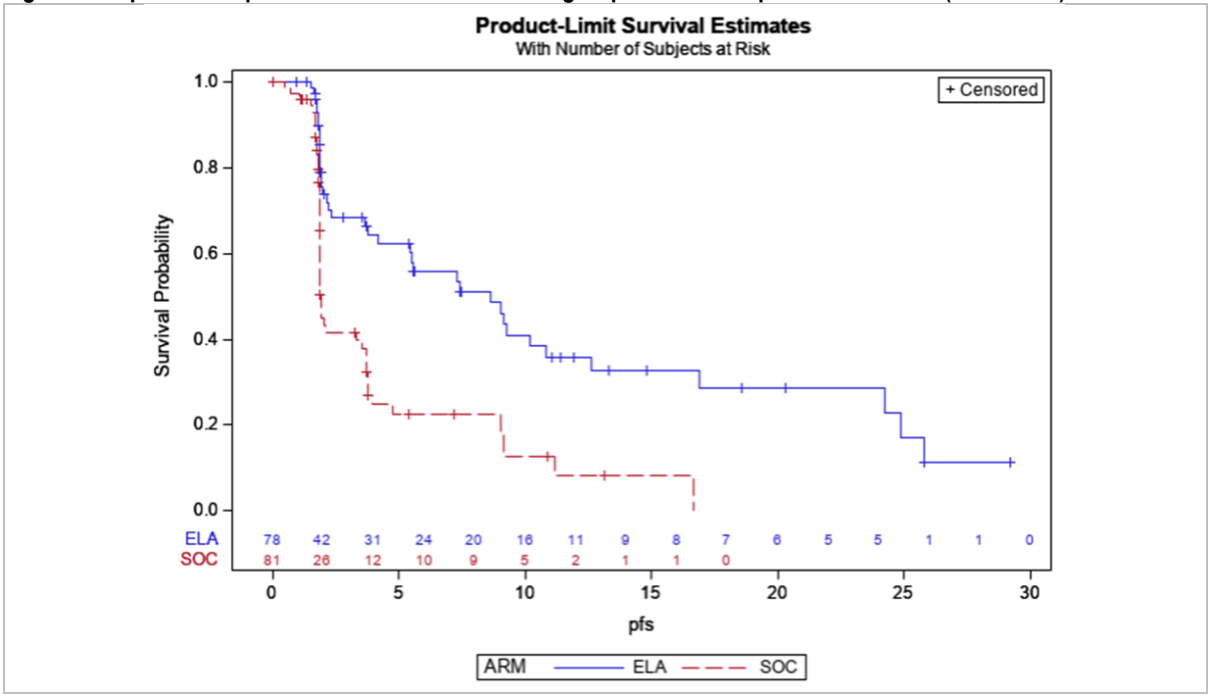
Source: compiled from:
Table 2.17: Key PFS and OS results from the EMERALD trial (ITT analysis), p86 of the resubmission.
Table 2.35: Blinded IRC-assessed PFS - All patients with ESR1 mutation who had received ≥12 months of prior ET + CDK4/6i - DCO 2nd September 2022, resubmission p109.
ESR1-Mutated Breast Cancer: Survival Analysis by CDK4/6 Inhibitor Duration (8 April 2026) – received during evaluation.
CI = confidence interval; CDK4/6i = cyclin dependent kinase type 4/6 inhibitor; ESR1 = estrogen receptor 1; ESR1-mut = ESR1 mutated; ESR1-mut-nd = ESR1 variant not detected; ET = endocrine therapy; HR = hazard ratio; ITT = intent to treat analysis population; mPFS = metastatic progression free survival; mo = month; NC = not calculable; NR = not reported; OS = overall survival; PFS = progression-free survival; SOC = standard of care.
[a] SOC in the EMERALD trial comprises of choice of aromatase inhibitor (AI) or fulvestrant monotherapy.
[c] Post hoc analysis used September 2022 data cut off for PFS. Median duration of follow-up was not stated for the ≥12 month subgroup at this cutoff.
[d] Test for interaction comparing the subgroups with either ≥12 months or ≤12 months prior treatment with a CDK4/6 inhibitor. A p value <0.05 would be considered statistically significant and suggest that ≥12 months prior treatment was a potential treatment effect modifier.
Note: p-values using stratified log-rank test.
Bold text indicates a statistically significant p-value
Information included in the previous submission is shaded blue.

6.28 In the resubmission, the HR for PFS in the *post hoc* defined EMERALD subgroup was statistically significant, corresponding to 6.7 months longer median PFS for elacestrant versus AI/FULV monotherapy. The median PFS was similar in the SOC arm for the whole trial population and the *post hoc* subgroup. There was no difference for OS in the *post hoc* subgroup, which was consistent with the prespecified analysis for the whole trial population and *ESR1* variant. Bardia et al. (2024) reported that the test for interaction between the group with prior ET+CDK4/6 inhibitor treatment <12 months versus the group with ≥12 months prior treatment was statistically significant (P=0.014) (however data for the subgroup receiving less than 12 months ET+CDK4/6i treatment were not presented in the publication or the resubmission). The ESCs recalled that it had previously considered that the comparator of AI/FULV monotherapy was not representative of SOC and is likely to overestimate the benefit for elacestrant.

6.29 The Kaplan-Meier plots for PFS and for OS in the *post hoc* EMERALD subgroup (presented with the corresponding SOC subgroup patients) are in Figure 3 and Figure 4, respectively. The curves showed reasonable separation for PFS but not for OS which

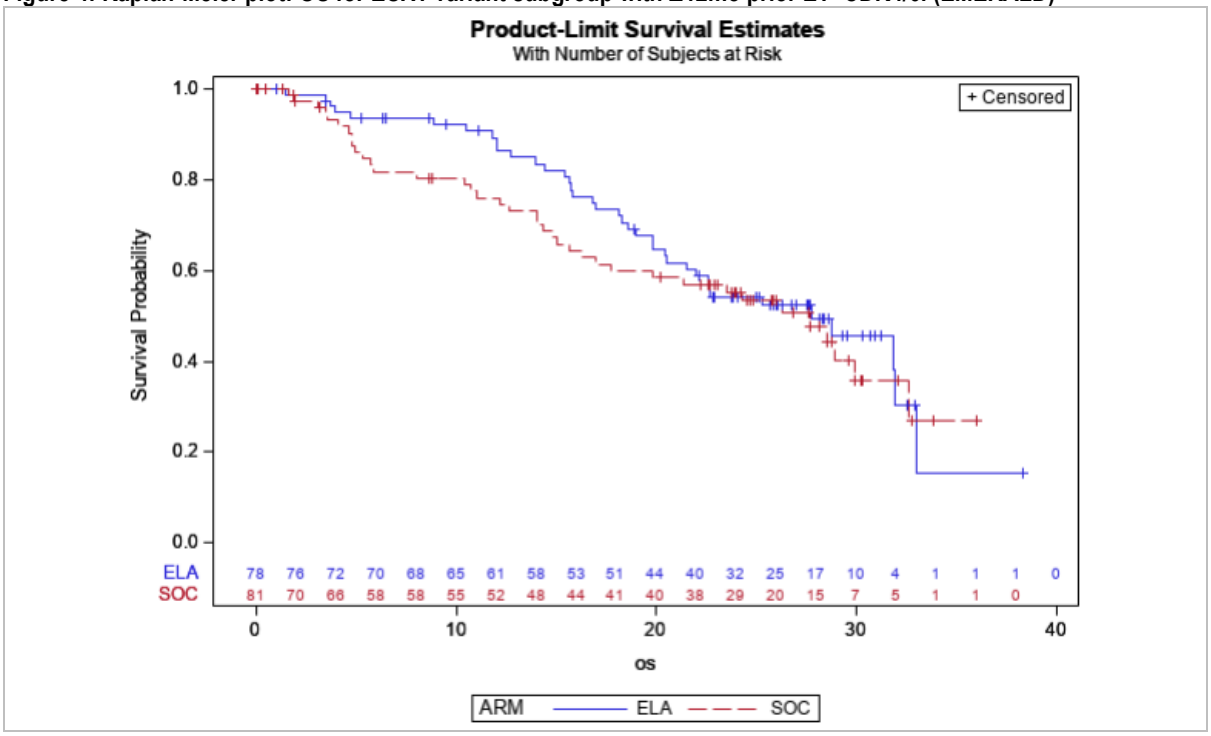
was similar to the plots for the whole trial population and *ESR1* variant prespecified subgroup.

Figure 3: Kaplan-Meier plot: PFS for *ESR1* variant subgroup with ≥12mo prior ET+CDK4/6i (EMERALD)



Source: Figure 2.13: Kaplan–Meier plot of IRC-assessed PFS in patients with ESR1 mutation who had received ≥12 months of prior ET + CDK4/6i | Elacestrant vs. SOC | DCO 2nd September 2022, resubmission p109.
BIRC = blinded independent review committee; CDK4/6i = cyclin dependent kinase type 4/6 inhibitor; ELA = elacestrant; ET = endocrine therapy; IRC = imaging review committee; mo = months; PFS = progression-free survival; SOC = standard of care.
Note: x-axis represents time in months.

Figure 4: Kaplan-Meier plot: OS for *ESR1* variant subgroup with ≥12mo prior ET+CDK4/6i (EMERALD)



Source: Figure 2.14: Kaplan–Meier plot for OS | All patients with ESR1 mutation who had received ≥12 months of prior ET + CDK4/6i | Elacestrant vs. SOC | DCO 2nd September 2022, resubmission p110.

CDK4/6i = cyclin dependent kinase type 4/6 inhibitor; ELA = elacestrant; ET = endocrine therapy; mo = months; OS = overall survival; SOC = standard of care.
Note: x-axis represents time in months.

ITC compared with EVE + EXE

6.30 The resubmission ITC used an unanchored matching adjusted indirect comparison approach (MAIC) (no common comparator given the comparator data were single arm).[8] The ITC examined the following arms:

- Elacestrant: N=78 *ESR1* variant EMERALD participants who had received ≥12 months prior ET+CDK4/6i regimen and received elacestrant in the trial. This subgroup is based on a *post hoc* analysis of EMERALD (see paragraph 6.13, 6.14).
- EVE + EXE: N=32 individuals from the Flatiron patient record database with at least 12 months prior CDK4/6 inhibitor treatment, who were all *ESR1* variant positive (see paragraph 6.31, 6.32).

6.31 The Flatiron Health (2024) analysis reported real world PFS (rwPFS) and real world OS (rwOS) in an *ESR1* variant cohort (N=47) which included patients with <12 months prior CDK4/6 inhibitor treatment (N=15) and patients with ≥12 months prior CDK4/6 inhibitor treatment (N=32) who were treated with EVE + EXE. The N=32 subgroup formed the resubmission ITC comparator arm – outcomes for rwPFS and rwOS in this subgroup are summarised in Table 10.

Table 10: rwPFS and rwOS for Flatiron participants, ESR1 variant, prior Tx ≥12 months CDK4/6i

Flatiron subgroup (*ESR1* variant, prior CDK4/6 inhibitor ≥12 months)	Events, n/N (%)	Median (95% CI)
rwPFS	27/32 (84.4)	4.57 (2.86, 6.93)
rwOS	20/32 (62.5)	17.97 (10.02, NR)

Source: Table 6. Unadjusted Kaplan-Meier median rwOS and rwPFS Estimates, p23-24 of Attachment 1.1.3 to the resubmission (Final Flatiron Report).
CDK4/6 = cyclin dependent kinase type 4/6; CI = confidence interval; N = number of participants in the group; n = number of participants with events; NR = not reported; rwPFS = real world progression-free survival; rwOS = real world overall survival; Tx = treatment.

6.32 The evaluation identified multiple concerns regarding the Flatiron Health data and report which affect the reliability of the data source. These included:

- The Flatiron data were from a longitudinal real-world, retrospective cohort study, representing a lower level of evidence than RCT or single arm prospective studies.
- The Flatiron data set represented very small patient numbers (likely due to low rates of *ESR1* testing in the database of over 3 million participants). No supporting analysis with participants agnostic to *ESR1* status was considered.

[8] The applicant affirms that, to the best of its knowledge at the time of making its request, the clinical data were only provided for the purposes of informing the PBAC consideration.

- Limited information was available on the methodological approach (no description of prespecified outcomes, statistical assumptions).
- No treatment information was available for the EVE + EXE regimens (dosing, duration, interruptions).

The PSCR stated that concerns regarding the Flatiron analysis had been addressed in additional materials (the Flatiron report) and the attrition table was provided; however, concerns regarding methodological transparency, data completeness, and potential selection bias remain.

6.33 In the MAIC presented in the resubmission the EMERALD subgroup participants were weighted (by age, sex, ECOG performance status where possible, prior lines of ET and prior chemotherapy in the metastatic setting), resulting in an effective sample size N=66.5 (85.3%) for elacestrant.

6.34 MAIC results are summarised for PFS and OS (before/after weighting) (Table 11).

Table 11: MAIC results before and after weighting: elacestrant vs EVE + EXE

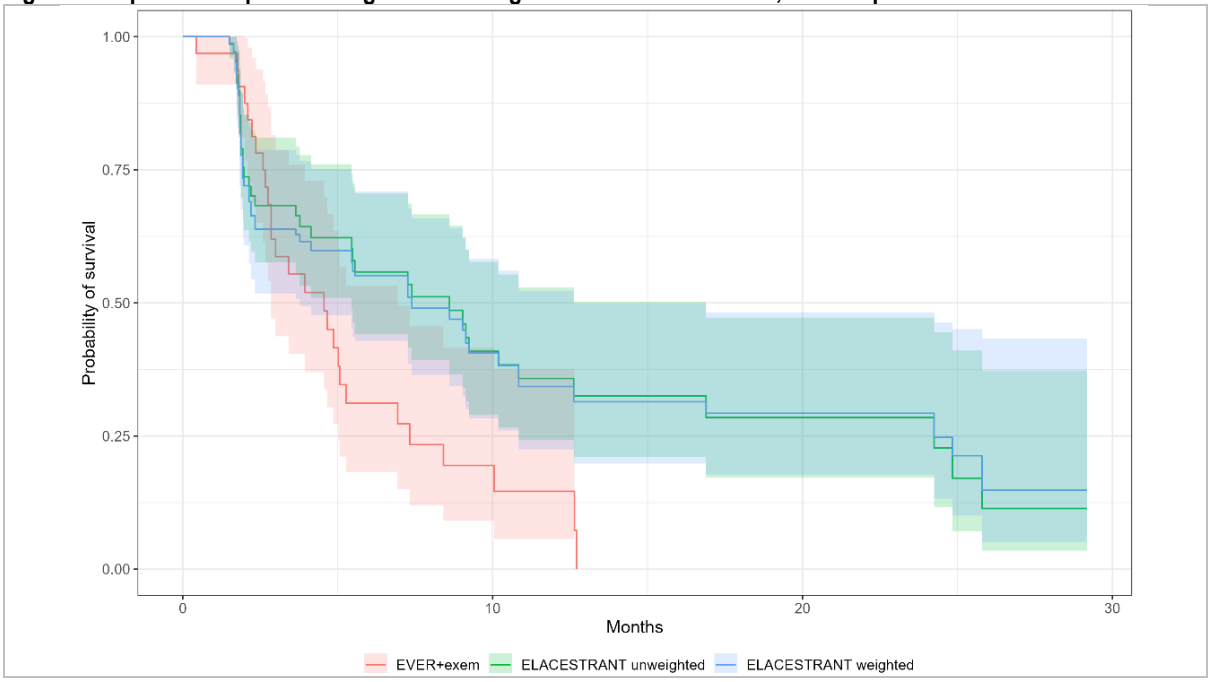
	Elacestrant (EMERALD)		EVE + EXE (Flatiron)		Elacestrant vs. EVE + EXE
	Events, n/N	Median (95% CI)	Events, n/N[a]	Median (95% CI)	HR (95% CI)
Before weighting: Event numbers, median values, and HRs					
PFS	39/78	8.61 (5.45, 16.89)	27/32	4.56 (2.85, 6.93)	**0.55 (0.33, 0.92)**
OS	38/78	27.73 (21.49, --)	20/32	17.96 (10.03, --)	0.62 (0.36, 1.08)
After weighting: Event numbers, median values, and HRs					
PFS	35.6/72.07 [b]	7.39 (3.78, 12.62)	27/32	4.57 (2.86, 6.93)	**0.59 (0.36, 0.96)**
OS	36.23/72.07 [b]	27.73 (20.53, --)	20/32	17.96 (10.03, --)	0.64 (0.35, 1.16)

Source: compiled during evaluation from:
Submission main body:
Table 2.39: MAIC hazard ratios | ESR1 mutation and ≥12 months of prior ET + CDK4/6i population
MAIC report (resubmission Attachment 3.1):
Table 18: Median PFS in population 2 – base case MAIC, p32
Table 19: Hazard ratio of PFS in population 2 – base case MAIC, p32
Table 21: Median OS in population 2 – base case MAIC, p36
Table 22: Hazard ratio of OS in population 2 – base case MAIC, p36
CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; *ESR1* = estrogen receptor 1 gene; ET = endocrine therapy; EVE+EXE = everolimus + exemestane; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; N = total number of participants; n = participants with events; OS = overall survival; PFS = progression-free survival.
a event numbers reconstructed from the MAIC report were assumed to remain the same before and after weighting for the comparator arm.
b Effective sample size in this table (N=72.07 [92.4%]) did not match that reported separately for the weighting (N=66.5 [85.3%]).
Values **in bold** are statistically significant. Note it was implied though not specifically stated in the MAIC report and the resubmission that MAIC outcomes (point estimates) were statistically significant if the upper bound of the confidence interval was less than 1.

6.35 The MAIC results reported a statistically significant improvement for PFS for elacestrant versus EVE + EXE. No difference was reported for OS.

6.36 Kaplan-Meier plots from the MAIC for PFS and OS for elacestrant versus EVE + EXE are presented in Figure 5 and Figure 6, respectively.

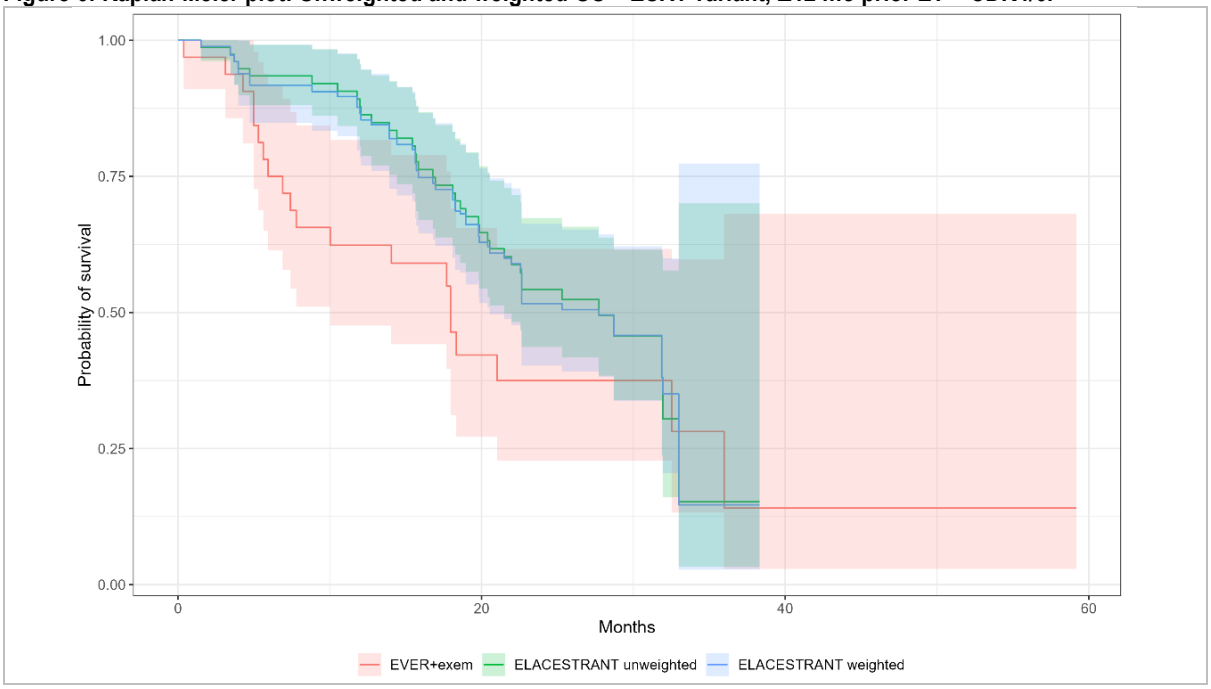
Figure 5: Kaplan-Meier plot: Unweighted and weighted PFS – *ESR1* variant, ≥12 mo prior ET + CDK4/6i



Source: Figure 2.16: Unweighted and MAIC-weighted PFS - ESR1 mutation and ≥12 months of prior ET + CDK4/6i population, resubmission p114.

CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ER = estrogen receptor; *ESR1* = estrogen receptor 1 gene; ET = endocrine therapy; EVER = everolimus; exem = exemestane; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival.

Figure 6: Kaplan-Meier plot: Unweighted and weighted OS – *ESR1* variant, ≥12 mo prior ET + CDK4/6i



Source: Figure 2.15: Unweighted and MAIC-weighted OS - ESR1 mutation and ≥12 months of prior ET + CDK4/6i population, resubmission p114.

CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ER = estrogen receptor; *ESR1* = estrogen receptor 1 gene; ET = endocrine therapy; EVER = everolimus; exem = exemestane; MAIC = matching-adjusted indirect comparison; OS = overall survival.

6.37 The curves for PFS intersected at around 3 months, which the MAIC report (p9, p23) contended was due to differences in data collection schedule (observational data vs RCT design), resulting in a violation of the proportional hazards assumption.

Intersecting curves showing violation of proportional hazards indicated that the point estimate from the analysis would be unreliable.

6.38 The evaluation and the ESCs noted multiple issues with the MAIC which limit the interpretation and reliability of the results presented in the resubmission. These included:

- The small group numbers in the source data for both arms (elacestrant and EVE + EXE), particularly notable given that ER+/HER2- breast cancer is a relatively common cancer type.
- The MAIC report did not include evidence addressing the likely extent of error due to unaccounted for covariates, as is strongly recommended for an unanchored MAIC.
- It was not stated whether analyses reported only prespecified objectives or if other *ad hoc* analyses were undertaken using different methodology or source data (potentially less favourable and thus selectively reported).
- The MAIC report included no comment on planned group sizes, statistical power, statistical significance, or reliability of the effect estimates based on the very small numbers in the comparator arms.
- No assessment of transitivity was included. The MAIC report included no consideration of exchangeability of the overall populations in each arm, nor impact of characteristics that could not be corrected for in the matching process due to lack of data. It was possible that residual differences between the MAIC arms remained such that the two populations were not exchangeable.

The PSCR acknowledged several of these issues and provided additional methodological clarification. However, acknowledging that many of these issues were could not be fully addressed as they reflect the available data, the ESCs considered that the fundamental concerns with the MAIC remain unchanged.

6.39 The ESCs considered that the above issues (6.38), particularly the low quality data for both intervention and comparator arms, constrained the value of the MAIC analysis. The evaluation and the ESCs considered that the PFS estimate for elacestrant versus EVE + EXE was not reliable even though the MAIC reported the estimate as statistically significant.

6.40 The EVE + ET arms of the evERA trial reported median PFS of 5.49 months (95% CI: 4.01, 5.59) and 5.45 months (95% CI: 3.75, 5.62), for the ITT and *ESR1* positive subgroup, respectively, which was longer than the EVE + EXE arm from Flatiron used in the MAIC.

Comparative harms

6.41 No new safety data or safety signals were reported for the resubmission. The previous submission reported that EMERALD patients in the elacestrant arm had a greater risk of experiencing treatment emergent adverse events (TEAEs) related to trial therapy (63.3% vs 43.5%), Grade ≥3 TEAEs (27.0% vs 20.9%) and TEAEs leading to interruption

(15.2% vs 5.2%). There were three patients with serious TEAEs related to treatment with elacestrant (2 patients had nausea, and 1 had vomiting, cholecystitis acute, decreased appetite, dehydration, and pulmonary embolism).

6.42 The most common Grade ≥3 TEAEs observed in the elacestrant arm were gastrointestinal (nausea) and musculoskeletal and connective tissue (back and bone pain) disorders. There were no deaths reported that were study drug related.

6.43 No ITC was presented for safety outcomes for elacestrant versus EVE + EXE.

6.44 Safety data were presented from EVE + EXE treatment in BOLERO-2 and BOLERO-6 for a naïve comparison with EMERALD. The BOLERO trials did not match the resubmission PICO, as patients had progressed on prior non-steroidal AIs (both trials pre-dated use of CDK4/6 inhibitors) and BOLERO patients were not tested for *ESR1* status.

6.45 In addition, the evaluation noted that clinical practice to manage adverse events (AEs) due to everolimus (e.g. stomatitis) has shifted since both BOLERO trials (e.g. management of stomatitis impacted by the adoption of prophylactic dexamethasone mouthwash following the SWISH trial, Rugo et al, Lancet Oncol 18(5) 2017). The evaluation considered that event rates observed in current clinical practice are likely to be lower for key events from BOLERO, therefore, any comparison would overestimate AEs in the comparator. BOLERO-2 was used in the economic model as a source of AE rates, and BOLERO-6 as a source of dose intensity for the EVE + EXE arm; however the evaluation considered that these values may not represent current practice. The ESCs noted that mucositis still occurs in clinical practice for patients treated with EVE + EXE.

6.46 The evaluation considered the event rates for EVE + EXE were unlikely to offer an accurate picture of current comparative safety using this the comparator arm. The evaluation and the ESC*s* considered that this, and other issues of exchangeability identified for the BOLERO trials suggests that general rates of AEs, SAEs, and Grade ≥3 AEs cannot be compared between trials.

6.47 The naïve comparison lacked individual events by preferred term that were of interest due to everolimus, such as stomatitis, rash, hyperglycaemia, and pneumonitis or, conversely, events characteristic of elacestrant such as those summarised above from the previous submission or reported for the *post hoc*. Overall, the ESCs considered that it was not possible to draw conclusions on comparative safety for elacestrant versus EVE + EXE based on the data presented in the resubmission.

Benefits/ harms

6.48 No benefits/harms table or consumer summary was compiled as there were no reliable estimates of PFS for comparative efficacy or AE rates for comparative safety.

Clinical claim

6.49 The resubmission described elacestrant in patients with an activating *ESR1* variant (identified by testing of ctDNA extracted by liquid biopsy) as superior in terms of effectiveness compared to EVE + EXE, for treatment of men and postmenopausal

women with ER+/HER2- mBC, who have disease progression following at least one line of ET, including a CDK4/6i for ≥12 months. The evaluation considered that this claim was not adequately supported. The ESCs considered that the claim was highly uncertain as the evidence was based on a small number of patients in both treatment arms, and the MAIC was associated with methodological limitations. However, on balance, the ESCs considered that elacestrant was likely superior to EVE + EXE in this population.

6.50 The submission described elacestrant in *ESR1* variant patients as "likely better tolerated" compared to EVE + EXE. The evaluation and the ESCs considered that this claim was not adequately supported based on the data presented. However, the ESCs considered that the safety profile of both treatments is well-established and, based on clinical experience, it is likely that elacestrant is at least noninferior to EVE + EXE in this population.

6.51 The PBAC considered that the claim of superior comparative effectiveness compared with EVE + EXE was not adequately supported by the data.

6.52 The PBAC considered that the claim of superior comparative safety compared with EVE + EXE was not adequately supported by the data, but considered elacestrant may have non-inferior comparative safety based on the established safety profiles of the medicines.

Claim of codependence

6.53 The biological rationale for *ESR1* testing as an eligibility criterion for elacestrant treatment was unchanged compared with the previous submission. The PBAC previously noted that although the test for interaction did not reach statistical significance there appeared to be minimal benefit in the non-*ESR1* subgroup and the clinical rationale and mechanism of action for elacestrant supported the claim that *ESR1* is likely to be a predictive biomarker for treatment with elacestrant. The ESCs previously considered the claim of codependence to be reasonable overall, but the extent of treatment effect variation to be uncertain (paragraph 6.32, elacestrant PSD, March 2025 PBAC meeting). The resubmission revised the patient population criteria and comparator – the claim was that an activating *ESR1* variant predicts improved treatment benefit with elacestrant versus EVE + EXE in patients with ER+/HER2– metastatic breast cancer who have had ≥12 months of prior ET + CDK4/6 inhibitor treatment (new elements underlined).

6.54 The claim of codependence as revised for the resubmission could not be evaluated in detail as the resubmission included no *ESR1* non-variant data in the analysis of elacestrant versus EVE + EXE. However, the ESCs recalled that they and PBAC and MSAC previously considered the claim of codependence to be reasonable, and the ESCs did not consider it necessary to re-prosecute the claim against the new comparator. See Table 8 and paragraph 6.22-6.25 for discussion of the evidence presented for the claim of codependence.

Economic analysis

6.55 The submission presented a cost-utility analysis, based on an indirect comparison of the EMERALD trial and Flatiron database comparing elacestrant and EVE + EXE in a population of patients with ER+/HER2- mBC who harbour an *ESR1* variant and who have disease progression following at least one line of ET, including a CDK4/6i. The economic evaluation was largely structurally consistent with the economic evaluation presented in the previous submission, with key differences being the updated patient population (specifying that patients must have had ≥12 months of ET + CDK4/6i) and comparator (EVE + EXE).

6.56 The ESCs noted that all issues identified with the clinical evidence presented in the resubmission (see paragraphs 6.38-6.39) flow through to the economic evaluation, in addition to further concerns regarding the model structure and assumptions. Table 12 provides a summary of the economic model structure and key inputs.

Table 12: Summary of model structure, key inputs, and rationale

Component	Summary
Comparison modelled	Test for *ESR1* variants available and treatment with elacestrant for patients with an activating *ESR1* variant vs testing not available and treatment with EVE+EXE for patients with an activating *ESR1* variant
Time horizon	10 years in the model base case vs 26 months follow up (median OS) in the EMERALD trial
Outcomes	LYG and QALYs
Methods used to generate results	Partitioned survival model (i.e. area under the curve)
Health states	PF, PD, and death TTD included to account for time on treatment
Cycle length	7 days
Test parameters	Not described Prevalence: 100% (implied as population only consists of patients with *ESR1* variants). Test accuracy/performance estimates (implied) Sensitivity = 100% Specificity = 100% Test failure rate = 0% Test uptake rate = 100%
Implications of false positive / negative results	Not described
Allocation to health states	Elacestrant: PFS, OS, and TTD KM data from cohort of patients in the EMERALD study with an *ESR1* variant treated with ≥12 months of prior ET + CDK4/6i. EVE + EXE: OS and PFS were derived from a cohort of patients with an *ESR1* variant treated with ≥12 months of prior ET + CDK4/6i in the Flatiron database. As the Flatiron database did not contain data on TTD, the model applied the HR for PFS between ELA and EVE + EXE (HR=0.59) to the KM estimate for TTD for elacestrant. Propensity score weights were applied to the EMERALD data to align with the Flatiron patients.
Extrapolation method	Independent parametric models were fitted to each treatment arm with Log-normal (PFS) and Log-logistic (OS) selected in the base case for elacestrant and Log-logistic (PFS) and Exponential (OS) selected in the base case for EVE + EXE, based on goodness of fit/visual inspection/assessment of the clinical plausibility of the extrapolation. TTD was not extrapolated (used KM data only). Truncation point from KM data to extrapolation was 28 months for both OS and PFS in both treatment arms (based on when survival data from EMERALD had matured) 31% of QALYs (and 9% of costs) in the elacestrant arm and 25% of QALYs and 13% of costs in the EVE + EXE arm occur in the extrapolated period.
Health related quality of life	A linear mixed-effects regression model was fitted to EQ-5D-5L data from the EMERALD trial with Australian tariffs applied. A baseline utility value, accounting for mean age of the population and proportion of patients receiving 2+ prior LOT was used for the PF state (excludes time-varying age and G3/4 AE decrements). Based on PBAC comments from the previous submission, to determine the PD utility value the model applied the utility decrement associated with disease progression reported in Lloyd et al 2006 (-0.272). Utility decrements associated with Grade 3/4 AEs reported in ≥2% of patients in both treatment arms were derived from the literature. Utility values used in model: PF=0.876 PD=0.604 Grade 3/4 AE decrement (sensitivity analysis only) = -0.001 (elacestrant), -0.002 (EVE+EXE)

Source: Table 3.2, p139 of the resubmission

AEs = adverse events; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; EQ-5D-5L = EuroQol 5 dimension 5 level; *ESR1* = estrogen receptor 1; ET = endocrine therapy; EVE = everolimus; EXE= exemestane; KM = Kaplan-Meier; LOT = line of therapy; LYG = life years gained; OS = overall survival; PBAC= Pharmaceutical Benefits Advisory Committee; PD = progressed disease; PF = progression free; PFS = progression-free survival; QALY = quality-adjusted life year; TTD= time to treatment discontinuation.

Components of the economic model unchanged from the previous submission are shaded in blue

6.57 The PBAC previously noted that the model structure did not capture patients at the point of testing as recommended in the PBAC Guidelines (Version 5.0). Although testing costs were included in the model for a single test, costs were underestimated as the proposed restriction allows testing at each episode of disease progression and no test scenarios were included in the economic model structure (paragraph 7.10, elacestrant PSD, March 2025 PBAC meeting). The ESC considered that this was partially addressed in the resubmission as the Sponsor updated the model to allow the user to modify the cost of the test (to investigate scenarios where multiple tests are required for some patients). However, the ESCs considered the model did not separately capture outcomes and costs for the arm of the clinical management algorithm in which retesting would occur for patients who initially test negative for *ESR1* variants, with elacestrant treatment for patients with activating *ESR1* variants at later lines of treatment. The model initiates with the drug population only (i.e. 47.7% patients with ER+/HER2- mBC that have received ≥12 months of prior ET + CDK4/6i, who test positive for an activating *ESR1* variant), not the test population as recommended by PBAC guidelines. However, the assumption of a 47.7% *ESR1* variant rate implies that the drug population includes all patients who will eventually test positive for *ESR1*, including those who initially test negative. The ESCs considered that the testing costs should be increased to account for retesting in patients who initially test negative.

6.58 The evaluation considered that the model implies that testing for *ESR1* variants in ctDNA extracted from blood plasma through NGS methodology (as used in the EMERALD trial which informs the model population) is associated with no false negative or false positive results, test uptake is 100%, test failure rate is 0%; these assumptions were not justified based on the clinical evidence presented.

6.59 The PBAC previously noted that the modelling approach was also not consistent with advice from PASC from the ratified MSAC PICO confirmation, which considered that cost modelling for both NGS and ddPCR methodology in the detection of *ESR1* variants should be included in the assessment (1782 Ratified PICO Confirmation, August 2024 PASC meeting) (paragraph 6.33, elacestrant PSD, March 2025 PBAC meeting). The ESCs considered although cost modelling for both NGS and ddPCR methodology was not included, the issue could be addressed via changing the test costs (see 6.57). As discussed in 'ESCs advice' to MSAC, the ESCs considered that an MBS fee of $550 for the *ESR1* ctDNA test was appropriate, however; the ESCs requested further clarification from the Department on the price difference between the suggested fee of $550 for the ctDNA test and the $400 standardised baseline fee for single gene, method-agnostic genetic testing items on the MBS.

6.60 The ESCs previously considered that the time horizon of 10 years applied in the base case may be reasonable, consistent with that recently accepted for trastuzumab deruxtecan for the treatment of mBC with disease progression (paragraph 6.45, elacestrant PSD, March 2025 PBAC meeting). The time horizon was unchanged in the resubmission and remains a key driver of model results (see Table 15).

6.61 Extrapolation of the key model outcomes of OS and PFS using independent parametric survival models (PSM) was set to begin when the survival data from EMERALD had matured; the resubmission stated that based on previous calculations, this occurred around 28 months. Applying a single truncation point for both OS and PFS outcomes was not appropriate and resulted in only KM data for PFS in the EVE + EXE arm being used as the truncation point was after the last observation (see **Error! Reference source not found.** below). Alternative truncation points using methods from Pocock et al 2002 (20% at risk) and Gebski et al 2018 were explored in sensitivity analyses (see Table 13). The choice of truncation point in the base case favoured elacestrant; using the '20% at risk' and Gebski et al 2018 methods increased the ICER by [redacted]% (see Table 15). TTD was not extrapolated in the model and relies on the KM data to estimate time on treatment in each arm. The ESCs considered that truncation at 28 months as per the resubmission base case remained problematic, as the truncation point occurs after the last observation for the EVE + EXE arm, such that only KM data are used (see **Error! Reference source not found.**). The ESCs considered that truncation using the Gebski et al 2018 methods was appropriate.

6.62 The resubmission stated that, overall, the log-normal parametric survival model was deemed appropriate to inform the base case assumptions for PFS in the elacestrant arm, based on landmark survival estimates and goodness-of-fit statistics. For the EVE + EXE arm, the resubmission stated that the log-normal parametric survival model was the most appropriate to extrapolate PFS, based on visual inspection, goodness-of-fit statistics, and long-term survival estimates. The evaluation considered that it would be more appropriate to adopt the log-logistic survival model (given better statistical fit and similar landmark survival analyses compared to Log-normal [adopted for the base case]) (Table 13); however, this made a minimal impact on the ICER (+[redacted]%).

Table 13: Predicted outcomes for PFS (using truncation points from Gebski et al 2018)

	Elacestrant	EVE + EXE	
	Base case (= Log-normal)	Base case (= Log-normal [ranked 3rd AIC/BIC])	Alternative (= Exponential [ranked 1st AIC/BIC]))
% alive and progression-free at 1-years	31.91%	9.01%	8.42%
% alive and progression-free at 2-years	14.30%	1.22%	1.80%
% alive and progression-free at 5-years	3.14%	0.03%	0.22%

Source: Developed during the evaluation using data from the revised economic workbook.
AIC= Akaike Information Criterion; BIC = Bayesian Information Criterion; EVE = everolimus; EXE = exemestane; PFS = overall survival
Note: Values in italics represent those calculated during the evaluation

6.63 The resubmission stated that, overall, the log-logistic parametric survival model was considered appropriate to inform the base case assumptions for OS in the elacestrant arm, based on visual inspection of the PSM versus the KM estimate, and long-term survival projections. For the EVE + EXE arm, the resubmission stated that the gamma parametric survival model was the most appropriate to extrapolate OS, based on visual inspection, goodness-of-fit statistics, and long-term survival projections. However, the evaluation and the ESCs considered that the exponential parametric survival model may be a plausible alternative, given the better model fit (based on AIC/BIC) and similar landmark survival estimates to the Gamma PSM (Table 14); this increased the ICER by [redacted]%.

Table 14: Predicted outcomes for OS (using truncation points from Gebski et al 2018)

	Elacestrant	EVE + EXE	
	Base case (= Log-logistic)	Base case (= Gamma [ranked 3rd AIC/BIC])	Alternative (= Exponential [ranked 1st AIC/BIC]))
% surviving at 5-years	15.71%	8.99%	10.43%
% surviving at 10-years	4.32%	0.71%	1.09%
% surviving at 20-years	1.08%	0.00%	0.01%

Source: Table 3.21, p219 of the resubmission.
AIC= Akaike Information Criterion; BIC = Bayesian Information Criterion; EVE = everolimus; EXE = exemestane; OS = overall survival.

6.64 The PBAC previously noted that the utility value for the PD state was inconsistent with prior submissions and the larger difference between the progression-free and progressed state utility values favoured elacestrant (paragraph 7.10, elacestrant PSD, March 2025 PBAC meeting). This has been addressed in the resubmission with the utility decrement associated with disease progression reported in Lloyd et al 2006 (-0.272) applied to the PF utility value derived from EQ-5D-5L data (Australian value set) from EMERALD (0.876) to determine the utility value for the PD health state (=0.604), consistent with methods used in prior PBAC submissions.

6.65 The resubmission stated that the expected cost of the proposed *ESR1* test is around $1,500. The sponsor proposed that only a portion of the testing cost be assigned to elacestrant since the utility of the test is not restricted to identifying patients eligible for PBS-listed elacestrant (assuming an NGS panel that can detect a variety of biomarkers useful in determining targeted treatment options, including PIK3CA, AKT1 and PTEN gene variants). The model apportioned 33% of the unit test cost to the elacestrant listing, then multiplied this by 2.10 (the number of tests required to identify one *ESR1* positive patient, based on the prevalence in the EMERALD trial [47.7%]). This amounted to a cost of $1,048.22 in *ESR1* variant testing per patient in the elacestrant arm. The evaluation and the ESCs considered that this was not appropriate; applying 100% of the unit test cost (resulting in a testing cost per patient in the elacestrant arm of $3,144.65) increased the ICER by [redacted]% (see Table 15). However, the ESCs noted that the revised test cost of $550 (reduced from $1,500) would be incorporated, which reduces the impact of correcting assumptions around test uptake (See Table 17).

6.66 A summary of the key drivers of the model is presented in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained
Incremental efficacy	Based on data from: Elacestrant - the subgroup with *ESR1* variant and treated with ≥12 months of prior ET + CDK4/6i from EMERALD EVE + EXE – data from Flatiron in matched patients	Likely to have a high impact. Alternative values could not be tested in sensitivity analyses.
Time horizon	10 years	High, favours elacestrant Reducing the time horizon to 5 years increased the ICER to $[redacted][1]/QALY gained (+[redacted]%)
Test costs	Apportions 33% of unit test cost of $1500 to elacestrant listing. No consideration of subsequent testing in patients who initially test negative.	Moderate, favours elacestrant Use of full unit cost for increased the ICER to $[redacted][1]/QALY gained (+[redacted]%)

Source: Developed during the evaluation
EVE = everolimus; EXE = exemestane; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life year.
The redacted values correspond to the following ranges:
[1] *$45,000 to < $55,000*

6.67 The results of the stepped economic evaluation (and comparison with results from the previous submission) are presented in Table 16.

Table 16: Results of the stepped economic evaluation

Step and component	Elacestrant	Comparator	Increment
Step 1: Trial based evaluation: Drug costs per LY over mean follow-up (18 months)			
Costs	$[redacted]	$7,086	$[redacted]
LYG	1.33	1.09	0.23
Incremental cost/extra LYG gained			**$[redacted][3]**
Step 2: incorporate additional costs			
Costs	$[redacted]	$13,614	$[redacted]
LYG	1.33	1.09	0.23
Incremental cost/extra LYG gained			**$[redacted][3]**
Step 3: Transformation of LYs into QALYs			
Costs	$[redacted]	$13,614	$[redacted]
QALYs	1.00	0.78	0.22
Incremental cost/extra QALY gained			**$[redacted][3]**
Step 4: Extend time horizon to 10 years, extrapolate OS, PFS, apply discounting of 5%			
Costs	$[redacted]	$16,883	$[redacted]
QALYs	1.90	1.28	0.62
Incremental cost/extra QALY gained			**$[redacted][4]**
Previous submission base case (March 2025 PBAC meeting)			
Costs	$[redacted]	$11,988	$[redacted]
QALYs	1.74	1.13	0.60
Incremental cost/extra QALY gained (base case)			**$[redacted][6]**

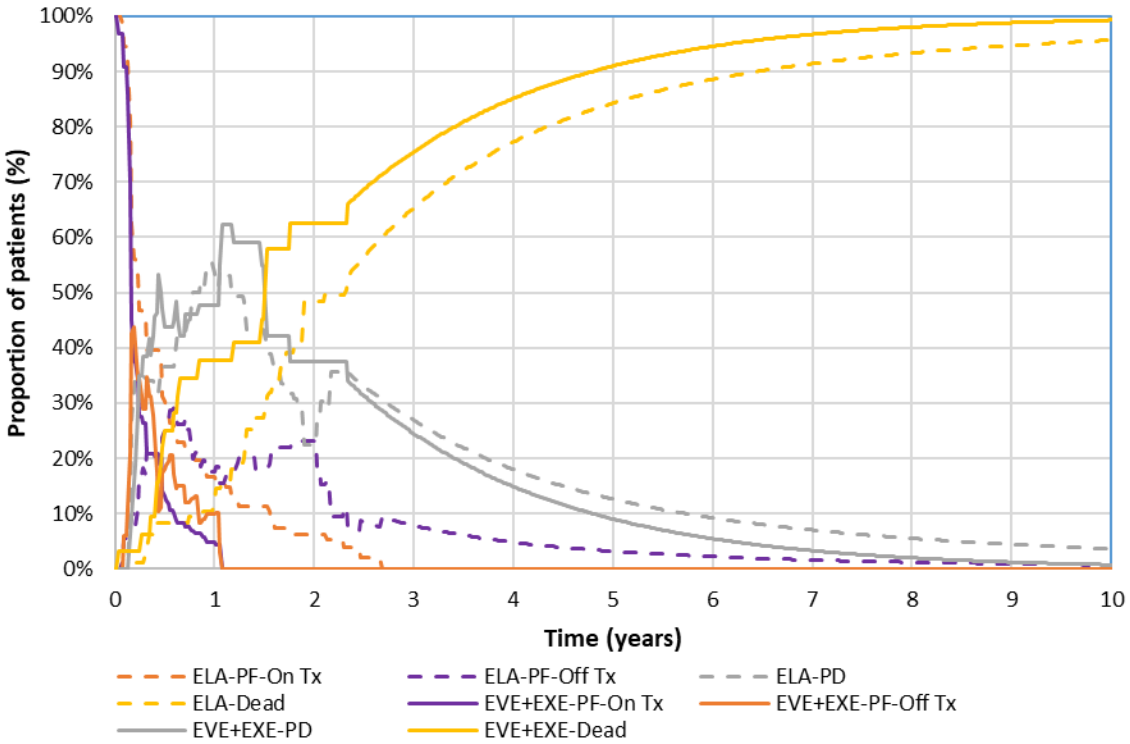
Source: Table 3.43, p239 of the resubmission.
EVE = everolimus; EXE = exemestane; LY= life year; LYG = life years gained; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PFS = progression-free survival; QALY = quality adjusted life year.
Results from previous submission are identified with blue shading
The redacted values correspond to the following ranges:
[1] *$25,000 to < $35,000*
[2] *$15,000 to < $25,000*
[3] *$95,000 to < $115,000*
[4] *$35,000 to < $45,000*
[5] *$45,000 to < $55,000*
[6] *$55,000 to < $75,000*

6.68 The ICER in the base case was $45,000 to < $55,000 per QALY gained. This compares to the base case ICER of $55,000 to < $75,000 per QALY gained in the previous

submission; the evaluator noted that this is mainly driven by the reduction in price for elacestrant. The ESCs noted that modelled QALYs were slightly higher for both elacestrant and the comparator arms compared to the previous submission, and the incremental QALYs were higher for the resubmission compared with the previous submission (0.62 vs 0.60). The ESC considered it was unclear whether this is clinically plausible given the change to the proposed eligible population and comparator. The ESC also noted that although the price for elacestrant is [redacted]% lower than in the previous submission, the reduced incremental cost ($[redacted] compared with $[redacted]) is also due to the higher cost for EVE + EXE.

6.69 The health state traces of the elacestrant and EVE + EXE arms over the model time horizon is presented in Figure 7.

Figure 7: Health state traces over model time horizon (base case)



Source: Sheet 'Results' from the revised economic workbook
ELA = elacestrant; EVE = everolimus; EXE = exemestane; PD = progressed disease; PF = progression-free

6.70 The results of key univariate/multivariate sensitivity analyses are summarised in Table 17. The combined impact of using truncation points for OS and PFS derived from Gebski et al 2018, applying the exponential parametric survival model for OS in the EVE + EXE arm and applying the full unit cost for the *ESR1* test as part of a multi-variate analysis increased the ICER to $45,000 to < $55,000 per QALY gained (+[redacted]%). However, the ESCs noted that the high level of uncertainty in the clinical evidence presented in the resubmission means that the modelled benefit is uncertain, resulting in ICERs that are highly uncertain. The pre-PBAC response accepted the multivariate sensitivity analysis as a revised base case. The pre-PBAC response proposed a price reduction to address residual uncertainty. The pre-PBAC response stated that this decreased the ICER to $35,000 to < $45,000 per QALY gained with the price reduction proposed in the pre-PBAC response.

Table 17: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change from base case
Base case	**$[redacted]**	**0.622**	**$[redacted][1]**	
Time horizon (base case 10 years)				
• 5 years	$[redacted]	0.505	$[redacted][1]	+[redacted]%
• 20 years	$[redacted]	0.683	$[redacted]	-[redacted]%
Truncation point KM data to extrapolation (base case =28 months PFS and OS for elacestrant and EVE + EXE)				
• 20% of patients at risk	$[redacted]	0.588	$[redacted][1]	+[redacted]%
• Gebski et al 2018 Criterion 1	$[redacted]	0.588	$[redacted][1]	+[redacted]%
Extrapolation PFS EVE + EXE (base case = independent Log-Normal)[a]				
• Log-logistic	$[redacted]	0.584	$[redacted][1]	+[redacted]%
Extrapolation OS EVE + EXE (base case = independent Gamma)				
• Exponential	$[redacted]	0.586	$[redacted][1]	+[redacted]%
Test cost (base case apportions 33% of unit cost of test [$1500] to elacestrant multiplied by 2.1, [based on prevalence of ESR1 variants in EMERALD trial of 47.7%] – total test cost per patient treated = $1,048.22)				
• 100% of unit cost for test applied	$[redacted]	0.622	$[redacted][1]	+[redacted]%
• 100% of unit cost for test [$550] applied (total test cost per +ve patient = $1,153.04)	$[redacted]	0.622	$[redacted][1]	<[redacted]%
• 100% of unit cost for test [$550] applied + assume 15% of patients require re-testing (total test cost per +ve patient = $1,326.00)	$[redacted]	0.622	$[redacted][1]	[redacted]%
Stepped multi-variate analysis				
• Truncation point = Gebski et al 2018 Criterion 1	$[redacted]	0.588	$[redacted][1]	+[redacted]%
• Extrapolation PFS EVE + EXE = Log-logistic	$[redacted]	0.584	$[redacted][1]	+[redacted]%
• Extrapolation OS EVE + EXE = Exponential	$[redacted]	0.547	$[redacted][1]	+[redacted]%
• 100% of $550 unit cost for test applied (total test cost per patient = $1,153.04)	$[redacted]	0.547	$[redacted][1]	+[redacted]%
• Multivariate analysis and pre-PBAC price reduction[b]	$[redacted]	0.547	$[redacted][c1]	-[redacted]%

Source: Table 3.40, pp243-244 of the resubmission.
EVE = everolimus; EXE = exemestane; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; OS = overall survival; PFS =progression-free survival; QALY = quality adjusted life year.
[a] As the truncation point from KM data to extrapolation in the base case was after all patients in the EVE + EXE arm had transitioned to PD or death, the impacts of different survival models was 0%. This has been corrected during the evaluation using the truncation point derived from Gebski et al 2018 criterion 1. The % ICER change is calculated based on an ICER of $45,000 to < $55,000/QALY gained
[b] Pre-PBAC response reduced the proposed AEMP to $[redacted] (345 mg vial).
[c] The ICER quoted in the pre-PBAC response was $35,000 to < $45,000 per QALY
The redacted values correspond to the following ranges:
[1] $45,000 to < $55,000

Drug cost/patient/course

6.71 A comparison of the drug cost/patient/course for elacestrant and EVE + EXE across trial, economic model and financial estimates is presented in Table 18.

Table 18: Drug cost per patient for proposed and comparator drugs

	Elacestrant Trial dose and duration	Elacestrant Model	Elacestrant Financial estimates	EVE + EXE Model	EVE + EXE Financial estimates
Mean dose	345mg/day (100%)	345mg/day (100%)	345mg/day (84%) 172mg (8%) 258mg (8%) [a]	EVE 10mg/day EXE 25mg/day	
Mean duration (days)	217.73	217.73	173.3 [b]	110.64	62.62 [c]
Compliance	98.2%	98.2%	95%	100%	95%
Scripts/patient/course[d]	7.67	7.67	5.88	3.95	2.12
DPMQ	$[redacted] (345 mg, 258 mg doses) $[redacted] (172 mg dose)			EVE: $1,738.71 (10 mg) EXE: $89.48 (25 mg)	
RDI	98.8%	98.8%	100%	EVE: 98.0% EXE: 100%	EVE: 100% EXE: 100%
Cost/patient/course[e]	$[redacted]	$[redacted]	$[redacted]	$7,086.48	$3,875.76

Source: Table 9, pp41-42, EMERALD – 12 month population CSR and data from the economic and financial workbooks.
DPMQ = Dispensed Price for Maximum Quantity; EVE = everolimus; EXE = exemestane; RDI = Relative dose intensity.
[a] Proportions based on data from Flatiron database
[b] Informed by data from Rugo et al 2026.
[c] Median duration of treatment reported in Flatiron (2.07 months)
[d] Calculated by mean duration of treatment ÷ max quantity per prescription [=28 days] x treatment compliance
[e] Calculated by scripts/patient/course x (DPMQ x RDI)
Note: No TTD data from Flatiron database (for EVE + EXE arm) was available; the economic model used the HR for PFS between ELA and EVE + EXE (HR=0.59) to the KM estimate for TTD for elacestrant

6.72 The cost per patient per course in the economic model using the price proposed in the pre-PBAC response was $[redacted].

6.73 While the drug cost/patient/course for elacestrant and EVE + EXE was consistent between the trial and economic model estimates, financial estimates for each drug were lower, owing to differences in duration of treatment and assumptions about compliance and relative dose intensity (RDI) applied. The submission did not provide any justification for the shorter treatment durations applied in the financial estimates compared with the model.

Estimated PBS usage & financial implications

6.74 This resubmission was not considered by DUSC. The resubmission adopted an epidemiological approach to estimate the number of incident and 'warehoused' (prevalent) patients with HR+/HER2- mBC (previously treated with ET + CDK-4/6i for ≥12 months) expected to initiate treatment with elacestrant; this was based on the proposed use of elacestrant primarily replacing EVE + EXE in the treatment pathway. While the general approach used for the financial estimates was consistent with the previous submission, the resubmission made several changes to data sources and methods for estimates of incidence and prevalent patients, as well as the estimated population prevalence of *ESR1* variants following PBAC's considerations from the previous submission.

6.75 A summary of the key inputs for the financial estimates is presented in Table 19.

Table 19: Estimation of number of treated patients

		Value	Year 1[a]	Source and comment
Incident patients				
A	Incident breast cancer cases (aged 18 to 100 years)		23,186	Projections from AIHW Cancer in Australia 2021 report. This was consistent with the data source used for incident breast cancer projections in recent PBAC submissions (Table 20, para 6.80, olaparib PSD, March 2023 PBAC and Table 24, para 6.98, capivasertib PSD, March 2025 PBAC).
B	Proportion HR+HER2-	69%		This was consistent with the value used in the PBAC submission for olaparib (Table 20, para 6.80, olaparib PSD, March 2023 PBAC meeting) and similar to the estimate applied in the PBAC submission for capivasertib (70%) (Table 24, para 6.98, capivasertib PSD, March 2025 PBAC).
C	Proportion mBC	25.9%		It was estimated that 5% of incident breast cancer cases are late stage, and 22% of incident early-stage patients will progress to late-stage disease (5% + (95% x 22%) = 25.9%). The PBAC previously agreed with DUSC that approximately 95% of incident breast cancer cases are Stage 1-3 (Table 20, para 6.80, olaparib PSD, March 2023 PBAC), meaning the estimate of 5% incident mBC patients is reasonable. The reference for the rate of metastasis was a study using NSW Cancer Registry data by Lord et al 2022
D	Proportion of HR+/HER2- mBC patients exposed to ET + CDK4/6i	82%		Based on analysis of ARORA, a multi-site Australian registry (Wong et al 2024). This was appropriate.
E	Proportion of patients on ET + CDK4/6i with 12+ months exposure	83%		Based on analysis of ARORA, a multi-site Australian registry (Javaid et al 2022). This was appropriate
F	Proportion of patients progressing while on ET + CDK4/6i	88%		Based on an analysis of the KARMA Australian registry. This was consistent with the value applied in the PBAC submission for capivasertib (Table 24, para 6.98, capivasertib PSD, March 2025 PBAC)
G	Uptake rate (testing)	Yr1: [redacted]% Yr2: [redacted]% Yr3+: [redacted]%		Assumption. The resubmission stated that testing uptake is expected to be small initially then will grow as education and awareness increases among clinicians and patients. The ESCs considered that not all of the 47.7% patients with *ESR1* variants would test positive initially, so applying a multiplication factor to account for a proportion of patients requiring retesting would be more appropriate.
H	Incident patients electing to test for *ESR1* variant		623	Calculation: (A x B x C x D x E x F x G)
I	Proportion *ESR1* mutated	47.7%		EMERALD trial. This is consistent with estimated population prevalence of ESR1 variants of between 40-50% (Brett et al 2021)
J	Incident patients testing positive for *ESR1* variants		297	Calculation: (H x I)
K	Uptake rate (treatment)	Yr1-2: [redacted]% Yr3: [redacted]% Yr4+: [redacted]%		Assumption. The resubmission stated that patients with an *ESR1* variant currently have no targeted treatment options and elacestrant is expected to pick up a large share of the market share initially but this will decrease over time as other targeted therapies enter the market. The ESCs considered that the decrease in uptake due to expected uptake of camizestrant was inappropriate and it would be more appropriate to apply a consistent [redacted]% update across all 6 years.

		Value	Year 1[a]	Source and comment
L	Incident patients initiating treatment		[redacted][1]	Calculation: (J x K)
Prevalent patients				
M	Prevalent patients with mBC (females aged 18 to 100 years)		21,640	BCNA mBC report for 2025 which provided estimates of prevalent female mBC patients in Australia on 2024 using AIHW data. The 2024 estimate of 20,800 prevalent cases were projected forward 2 years using a 2% growth rate. This was reasonable.
N	Prevalent patients electing to test for *ESR1* variant		[redacted][2]	Calculation: (M x B x D x E x F x G) = [redacted][2] – assumed to be distributed over first 3 years (year 1: [redacted][2] [50%], year 2: [redacted][2] [30%], year 3: [redacted][1] [20%])
O	Prevalent patients testing positive for *ESR1* variant		[redacted][2]	Calculation: (N x I)
P	Prevalent patients initiating treatment		[redacted][1]	Calculation: (O x K)
	Total patients tested		[redacted][2]	Calculation: (H [incident patients] + N [prevalent patients])
	Total patients treated		[redacted][2]	Calculation: (L [incident patients] + P [prevalent patients])

Source: Tables 4.1-4.2, pp250-252 of the resubmission
1L = first line; AI = aromatase inhibitor; AIHW = Australian Institute of Health and Welfare; BCNA = Breast Cancer Network Australia; CDK4/6i = cyclin dependent kinase 4/6 inhibitors; DUSC = Drug Utilisation sub-committee; *ESR1* = estrogen receptor 1 gene; ET = endocrine therapy; HR+ = hormone receptor positive; HER2- = human epidermal growth factor 2 negative; mBC = locally advanced or metastatic breast cancer; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public summary document; Yr = year.
[a] Number of treated patients estimated at each step in Year 1 of the financial estimates.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*

6.76 Overall, the evaluation considered that the data sources and parameter values applied in the utilisation and financial estimates in the resubmission were appropriate; however, applying the proportion of patients with HR+/HER2- mBC (as opposed the ER+/HER2- as specified in the PBS restriction) risks overestimating the number of incident and prevalent patients. While most HR+/HER2- breast cancers are reported to be ER+[9] (meaning the impact is likely to be minor), no estimates which differentiate HR+/HER2- breast cancers by ER+/PR+ were identified. The resubmission assumed that the uptake rate of elacestrant is expected to diminish with the expected introduction of camizestrant in the future. However, the ESCs considered it was not appropriate to include this assumption in the financial estimates and recommended revising the financial estimates with no drop-off in uptake rate.

6.77 The ESCs noted the new MBS testing fee of $550 (rather than $1500, see paragraph 6.65) should be incorporated.

6.78 The resubmission claimed that elacestrant will substitute for other mBC treatments, primarily EVE + EXE (assumed 100% substitution). The median duration of EVE + EXE treatment from the Flatiron database (2.07 months) was applied, with compliance assumed to be equal to elacestrant (95%). Neither EVE nor EXE has an SPA. The evaluation considered that this was reasonable given the clinical claims that

[9] Breast Cancer Network Australia. HR+ breast cancers. Available from: https://www.bcna.org.au/resources/about-breast-cancer/types-and-subtypes-of-breast-cancer/hormone-receptor-positive-breast-cancers

elacestrant has superior efficacy than EVE + EXE and is as tolerable in terms of safety. However, as noted in paragraph 5.7, based on a 10% PBS sample analysis of treatments used by patients progressing from CDK4/6i treatment for ER+/HER2- mBC, there are a range of subsequent therapies used, with EVE + EXE only estimated to be used by 3% of patients. As such the evaluation and the ESCs considered that these estimates are highly uncertain.

6.79 A summary of the estimated use and financial implications to the health budget (MBS/PBS/RPBS) associated with the listings of the co-dependent therapies is presented in Table 20.

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of test for *ESR1* variants						
Number of patients tested	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients likely to receive a positive test result	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated extent of use of elacestrant						
Number of patients likely to be treated with proposed drug	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]
Number of scripts dispensed [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of test for *ESR1* variants to the MBS						
Cost to the MBS less copayments [b]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications of elacestrant to the PBS/RPBS						
Cost to PBS/RPBS less copayments	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Estimated financial implications for EVE + EXE						
Cost to PBS/RPBS less copayments	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net financial implications (resubmission)						
Net cost to PBS/RPBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net financial implications (pre-PBAC response)						
Net cost to PBS/RPBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to MBS	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Net cost to PBS/RPBS/MBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Previous submission (March 2025 PBAC meeting)						
Net cost to PBS/RPBS	$[redacted][6]	$[redacted][4]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Net cost to PBS/RPBS/MBS	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][6]	$[redacted][6]

Source: Sheets '2a.Patients - incident' – '7.Net changes – MBS'' to of the revised Excel financial workbook

ESR1 = estrogen receptor 1 gene; EVE = everolimus; EXE = exemestane; MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Reparation Pharmaceutical Benefits Scheme.

[a] Assuming 5.88 scripts per year as estimated by the resubmission.

[b] 85% benefit and greatest permissible gap (=$104.50) applied to proposed test cost for *ESR1* variants (all out of hospital services)

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *< 500*

[3] *$0 to < $10 million*

[4] *$10 million to < $20 million*

[5] *net cost saving*

[6] *$30 million to < $40 million*

[7] *$20 million to < $30 million*

6.80 The submission estimated the net cost to the health budget of listing was $10 million to < $20 million in Year 6, and a total of $90 million to < $100 million in the first 6 years of listing. This decreased to $90 million to < $100 million based on the revised price for elacestrant in the pre-PBAC response. This compares to a net cost to the health budget of $100 million to < $200 million in the first 6 years of listing in the previous submission. The evaluation noted that the reduction in net cost in the resubmission compared to the previous submission is due to reductions in estimates of incident patients (due to the updated restriction for testing and treatment that patients require ≥12 months prior ET + CDK4/6i and estimates from AIHW instead of PBS 10%), reductions in estimates of patients who test positive for *ESR1* variants and are eligible for treatment with elacestrant (due to population prevalence of *ESR1* variants of 47.7% being correctly applied in the resubmission) and price reduction of elacestrant (approximately 14% reduction).

6.81 However, the evaluation and the ESCs considered that the net costs to the MBS reported in the resubmission may be underestimated, as methods used assume that patients test positive on their first test after disease progression following 1L therapy and that test accuracy is 100% and test failure is 0% (i.e. each patient receives one test only). This is not consistent with the total prevalence of *ESR1* positive patients in EMERALD, including those with disease progression following 1L or 2L therapy, the proposed MBS restriction (which places no limits on the frequency or number of tests), or estimates of test accuracy provided. The ESCs considered that it would be appropriate to apply a multiplier to the financial estimates to account for patients who undergo *ESR1* testing more than once. The ESCs noted that the total assumed *ESR1* prevalence of 47.7% is consistent with EMERALD and therefore no changes were required to the estimated proportion of patients eligible for treatment with elacestrant.

6.82 The evaluation noted that all identified sources of uncertainty tested in sensitivity analyses made a moderate-large impact on the net costs to the health budget, with changes in the expected uptake of testing making the largest impact (-[redacted]%/+[redacted]% with a -[redacted]%/+[redacted]% change in uptake of testing). Other sources of uncertainty identified in the evaluation that were not able to be explored in sensitivity analyses include applying the proportion ER+/HER2- patients only (not HR+/HER2- as applied in the resubmission- see paragraph 6.76), uncertainty around test accuracy and the extent to which elacestrant may substitute for other treatments for mBC (see paragraph 6.78).

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of elacestrant for the treatment of estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) locally advanced or metastatic breast cancer with an activating estrogen receptor 1 (*ESR1*) variant in patients who have disease progression following at least one line of endocrine therapy, including at least 12 months of treatment with a cyclin-dependent

kinase 4/6 inhibitor (CDK4/6i). The PBAC considered that the resubmission provided improved clarity regarding the clinical place for elacestrant, which was for a small number of patients. The PBAC considered that while the proposed comparator in the resubmission (everolimus + exemestane, EVE + EXE) was more appropriate than endocrine monotherapy (the comparator in the March 2025 submission), it remained an inadequate representation of the SOC second line (2L) treatment options for the proposed patient population. The PBAC considered the indirect comparison presented as clinical evidence was of poor quality and therefore did not adequately support the clinical claim that elacestrant is more effective than EVE + EXE. The PBAC considered that, given the limitations of the clinical evidence, the clinical outcomes in the economic model were not supported and elacestrant was not cost-effective at the proposed price.

7.2 The primary reason for this outcome was the limitations with the clinical evidence. The PBAC considered the clinical evidence that compared elacestrant and EVE + EXE was unreliable and therefore the PBAC did not accept that elacestrant has superior comparative effectiveness compared with EVE + EXE.

7.3 The PBAC acknowledged the comments from health professionals and professional organisations, which expressed a preference for oral treatments that require fewer visits to specialist clinics and a preference for treatments that have fewer side-effects and are less invasive. The PBAC considered that for some patients there is a moderate clinical need for alternative treatments with fewer adverse events, to allow patients to avoid or delay the use of chemotherapy. However, the PBAC noted that there are several alternative PBS-listed treatment options for this group of patients.

7.4 The PBAC considered the revisions to the requested restriction proposed in the resubmission were appropriate and consistent with its previous advice (see paragraph 7.3 elacestrant PSD, March 2025 PBAC meeting).

7.5 The PBAC considered that the resubmission provided improved clarity regarding the clinical place for elacestrant by proposing to restrict the population eligible for elacestrant to patients who have received at least 12 months of prior CDK4/6i treatment. The PBAC agreed with the resubmission that this is likely to identify patients most likely to be sensitive to targeted endocrine therapy that address acquired resistance mechanisms, such as elacestrant.

7.6 The PBAC noted that in the resubmission EVE + EXE was chosen to represent 2L SOC treatment in the target population. The PBAC considered that the proposed comparator in the resubmission was more appropriate than ET monotherapy (as used in the March 2025 submission) as it is an active therapy with improved efficacy compared to ET monotherapy. However, the PBAC noted that there are several other 2L treatment options including capecitabine (chemotherapy) and capivasertib + fulvestrant. The PBAC considered there may also be some use of fulvestrant monotherapy for the endocrine sensitive population, but reaffirmed that fulvestrant and other ET monotherapy was not representative of SOC as other viable options would be preferred for many patients due to improved efficacy compared with ET monotherapy (para 7.6, elacestrant PSD, March 2025 PBAC meeting). Overall, noting its low use after CDK4/6i treatment based on the PBS data analysis (see paragraph

5.7), the PBAC considered EVE + EXE was not broadly representative of the treatments used in the proposed population.

7.7 The PBAC noted the clinical evidence for elacestrant relied on in the resubmission was from a small *post hoc* subgroup of the EMERALD trial, including 78 patients who had an *ESR1* variant and had ≥ 12 months prior treatment with CDK4/6i + ET. The elacestrant *post hoc* identified subgroup had superior PFS compared with the corresponding SOC subgroup (n=81). However, there was no statistically significant improvement in OS in the subgroup, which was consistent with results in the whole trial population. The PBAC recalled it previously considered that the EMERALD trial is likely to overestimate the benefit for elacestrant compared to SOC as the comparator arm was suboptimal and expected to be ineffective for a substantial proportion of patients (paragraph 7.7, elacestrant PSD, March 2025 PBAC meeting).

7.8 The PBAC noted that the clinical comparison of elacestrant and EVE + EXE was based on an unanchored MAIC that compared the elacestrant *post hoc* identified subgroup from the EMERALD trial with 32 patients in the Flatiron Health database who had an *ESR1* variant and at least 12 months of prior treatment with CDK4/6i + ET. The MAIC weighted the elacestrant *post hoc* identified subgroup by age, sex, ECOG performance status where possible, prior lines of ET and prior chemotherapy in the metastatic setting, resulting in an effective sample size of 66 patients. The adjusted and unadjusted MAICs reported that elacestrant was associated with statistically significant improvements in PFS but no difference in OS. The PBAC considered the results of the unanchored MAIC were unreliable because it was based on a very small number of patients in each arm and had a very high risk of bias from the selection of patients included in the analysis and unknown and unmeasured confounding factors. The PBAC considered that these limitations in the MAIC and the data informing it reduced its confidence that the results from the unanchored MAIC were due to true differences in clinical effectiveness between elacestrant and EVE + EXE and considered that the claim of superior comparative effectiveness compared with EVE + EXE was not adequately supported by the data.

7.9 The PBAC considered the resubmission's claim that elacestrant is likely better tolerated than EVE + EXE was not supported by the data presented, which did not allow meaningful comparison of safety outcomes. However, the PBAC considered elacestrant may have non-inferior safety to EVE + EXE based on the established safety profiles of the medicines.

7.10 The PBAC noted a cost-utility analysis was presented in the resubmission. The PBAC noted that the structure of the economic model was similar to that for the previous submission, however due to the different comparator (EVE + EXE), and revised population (at least 12 months of prior CDK4/6i treatment), the efficacy data informing the model were based on the MAIC. The PBAC considered the results of the cost-utility analysis could not be used to assess the cost-effectiveness of elacestrant because the underlying clinical evidence was not reliable. The PBAC noted that potential alternative therapies, such as EVE + EXE, fulvestrant and capecitabine are substantially less costly compared to the price proposed for elacestrant in the pre-

PBAC response. The PBAC considered that elacestrant was not cost-effective at the proposed price.

7.11 The PBAC noted the resubmission's estimated lower utilisation of elacestrant, partly due to the proposed population being limited to patients who had received at least 12 months of treatment with a CDK4/6i. The PBAC considered the estimates of utilisation were highly uncertain. The PBAC considered the financial implications would depend on the extent to which elacestrant would replace other therapies. The PBAC considered this would not be limited to EVE + EXE as it accounts for a small proportion of treatments used after CDK4/6i therapy. The PBAC considered that it was not appropriate for uptake estimates to assume the availability of camizestrant, which has not yet been considered by the PBAC. The PBAC considered that the treatment duration, compliance and dose intensity should be consistent with the economic model. The PBAC also noted that there were uncertainties in the uptake of testing and use of *ESR1* testing which would impact on the utilisation of elacestrant and noted that these would be considered by the MSAC.

7.12 The PBAC considered a resubmission for elacestrant should provide higher quality clinical evidence demonstrating the magnitude of benefit for elacestrant over SOC, which could inform an economic model demonstrating the cost-effectiveness of elacestrant compared to effective alternative therapies. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.