

5.06 FULVESTRANT, Injection 250 mg in 5 mL pre-filled syringe, Faslodex[®], AstraZeneca Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested a streamlined listing for fulvestrant monotherapy for first-line and second-line endocrine-based treatment of patients with non-premenopausal, hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (ABC).
- 1.2 The submission presented a cost-effectiveness analysis of fulvestrant versus anastrozole for first-line treatment. A cost-minimisation analysis of fulvestrant versus everolimus + exemestane (EVE+EXE) was presented for the second-line treatment of patients who have progressed in the first-line setting.

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

Component	Description
Population	HR+, HER2- ABC
Intervention	Fulvestrant (Faslodex)
Comparator	First-line: Primary – Nonsteroidal aromatase inhibitors (anastrozole, letrozole) Secondary – Nonsteroidal aromatase inhibitors + CDK4/6 inhibitors (palbociclib, ribociclib)
	Second-line: Everolimus + exemestane
Outcomes	OS, PFS, ORR, Safety
Clinical claim	First-line: In HR+, HER2- ABC, fulvestrant has superior efficacy in terms of OS and non-inferior safety compared with non-steroidal aromatase inhibitors.
	Second-line: In HR+, HER2- ABC, fulvestrant is non-inferior in terms of OS and has superior safety compared with everolimus in combination with exemestane

HR+, hormone receptor positive; HER2-, human epidermal growth factor receptor 2 negative; ABC, advanced breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression free survival
Source: Table 1.1, p14 of the submission, p143 of submission

2 Background

- 2.1 Fulvestrant is not currently listed on the PBS and has not previously been considered by the PBAC. A request for listing of ribociclib in combination with fulvestrant for the treatment of patients with HR+, HER2- advanced breast cancer was also considered at the July 2020 PBAC meeting.

Registration status

- 2.2 Fulvestrant monotherapy under the brand name, Faslodex® (AstraZeneca), was approved by the Therapeutic Goods Administration (TGA) in March 2006 for the treatment of postmenopausal women with HR+ advanced/metastatic breast cancer with progressive disease following prior tamoxifen therapy. However, at the time of the PBAC meeting, fulvestrant was not registered as monotherapy in the first-line setting.
- 2.3 The sponsor of this submission (AstraZeneca) submitted a TGA application for amendment of the existing fulvestrant indication in April 2020. At the time of the PBAC meeting, no TGA documents were available. The TGA Delegate's Overview is not expected to be available until March 2021, and the indication is not anticipated to be amended until April 2021.
- 2.4 The sponsor's proposed TGA indication is postmenopausal women with HR+, locally advanced or metastatic breast cancer who:
- have not previously been treated with endocrine therapy, or
 - have progressive disease following prior tamoxifen therapy.
- 2.5 The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approved different indications in the second-line (progressive disease) setting. The requested TGA indication is similar to the EMA indication, which was updated in 2018 to include monotherapy for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:
- not previously treated with endocrine therapy, or
 - with disease relapse on or after adjuvant antiestrogen therapy, or disease progression on antiestrogen therapy (i.e. tamoxifen).
- 2.6 However, the indication approved by the FDA in the progressed disease setting is broader, as it also allows use following endocrine therapy (which includes aromatase inhibitors (AIs) as well as tamoxifen). The FDA indication (which was updated in 2017) is for:
- HR+, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy, or
 - HR+ advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
- 2.7 The above information relates to use of fulvestrant as a single-agent. The TGA indications for ribociclib and abemaciclib include combination use with fulvestrant and the TGA indication for palbociclib includes combination use with fulvestrant in patients who have received prior therapy. Consequently, combination use is considered to be "on-label", although combination use was not requested in this submission.

Regulatory history of fulvestrant

- 2.8 The initial approval of fulvestrant by the FDA and EMA (2002) was based on two studies that recruited women with metastatic HR+ breast cancer, who had progressed on tamoxifen. The comparison was fulvestrant 250 mg/month versus anastrozole 1 mg/day. The two studies established non-inferiority of fulvestrant 250 mg versus anastrozole 1 mg, after progression on tamoxifen.
- 2.9 It was subsequently found that 500 mg/month was just as tolerable, and more effective, than 250 mg/month (CONFIRM study) and the dosing was updated to 500 mg/month. CONFIRM recruited women who had progressed on endocrine therapy (mainly AIs).
- 2.10 Subsequently, FALCON was conducted in the first-line setting comparing fulvestrant 500 mg/month versus anastrozole 1 mg/day. There was a trend towards improved OS that was not statistically significant. Both the EMA and FDA updated the indication to include first-line use (500 mg), based on FALCON.
- 2.11 The FDA updated the second-line indication (originally after tamoxifen) to include use after any endocrine therapy (i.e., tamoxifen or AI). This was based on an indirect comparison across the original registration studies (2002, after tamoxifen) and CONFIRM (which compared the 250 mg and 500 mg doses, after AI). The EMA did not update the second-line indication.
- 2.12 The TGA single-agent indication is currently the same indication that was initially approved: second-line use after tamoxifen.

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

3 Requested listing

- 3.1 The submission proposed listing 3 separate Authority Required (Streamlined) treatment phases (initial, continuing and grandfather treatment). The Secretariat considered that all 3 treatment phases could be covered by one restriction and the listing as suggested by the Secretariat is outlined below.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	AEMP	DPMQ	Proprietary name and manufacturer
Fulvestrant, 250mg/5mL, solution for injection	1	2	5	\$828.69 Published \$ █████ SPA	\$927.37 Published \$ █████ SPA	FASLODEX, AstraZeneca Australia Pty Ltd
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency)						
Indication: Locally advanced or metastatic breast cancer						
Clinical criteria:						

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The condition must be hormone receptor positive AND The condition must be human epidermal growth factor receptor 2 (HER2) negative AND The condition must be unresectable
Population criteria: Patient must not be pre-menopausal.
Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
Administrative Advice: 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 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Special pricing arrangements apply

AEMP = approved ex-manufacturer price; DPMQ = dispensed price per maximum quantity
\$ SPA, price related to proposed special pricing arrangement

- 3.2 A special pricing arrangement was proposed, with an effective AEMP of \$ [REDACTED]. The submission stated that generic versions of fulvestrant may be available in Australia, after market exclusivity expires in [REDACTED], which if PBS listed would lead to a 25% reduction in the price of fulvestrant.
- 3.3 The ESC and the PBAC considered that the restriction should require that the condition be unresectable, consistent with the patient population included in the clinical evidence presented. The pre-PBAC response stated that the sponsor was willing to accept the PBAC's advice on this aspect of the restriction.
- 3.4 The requested PBS restriction is line-agnostic and is broader than the current and proposed TGA indications. The requested TGA indication would not allow use in patients who have progressive disease on or after CDK4/6 inhibitors and/or aromatase inhibitors (as the proposed TGA indication in progressive disease remains unchanged and requires prior use of tamoxifen). If used in line with the proposed TGA indication, there is likely to be only a limited place for second-line fulvestrant, as tamoxifen is no longer considered standard first-line therapy, although there may be some use in subsequent lines. As such, the PBAC noted that the majority of use in second (and subsequent) lines will be outside the requested TGA indication, regardless of the requested update to the TGA indication. The PBAC noted that the proposed listing was consistent with the NCCN and ESMO guidelines in not specifying prior treatments and noted that the current listing for exemestane does not specify prior treatments.
- 3.5 While the evidence presented is for use as fulvestrant monotherapy, the proposed restriction would not specifically prohibit use in combination with other medicines, such as CDK4/6 inhibitors. However, such use would be prohibited in the CDK4/6 inhibitor restrictions, which state treatment must be in combination with anastrozole or letrozole.

- 3.6 The submission estimated that < 500 patients on a Patient Access Program would be eligible to receive PBS-funded treatment at the start of 2021 and requested a grandfather listing for these patients. The Secretariat noted that such patients would be able to transition to PBS supply under the proposed PBS eligibility criteria without requiring a separate grandfather listing.

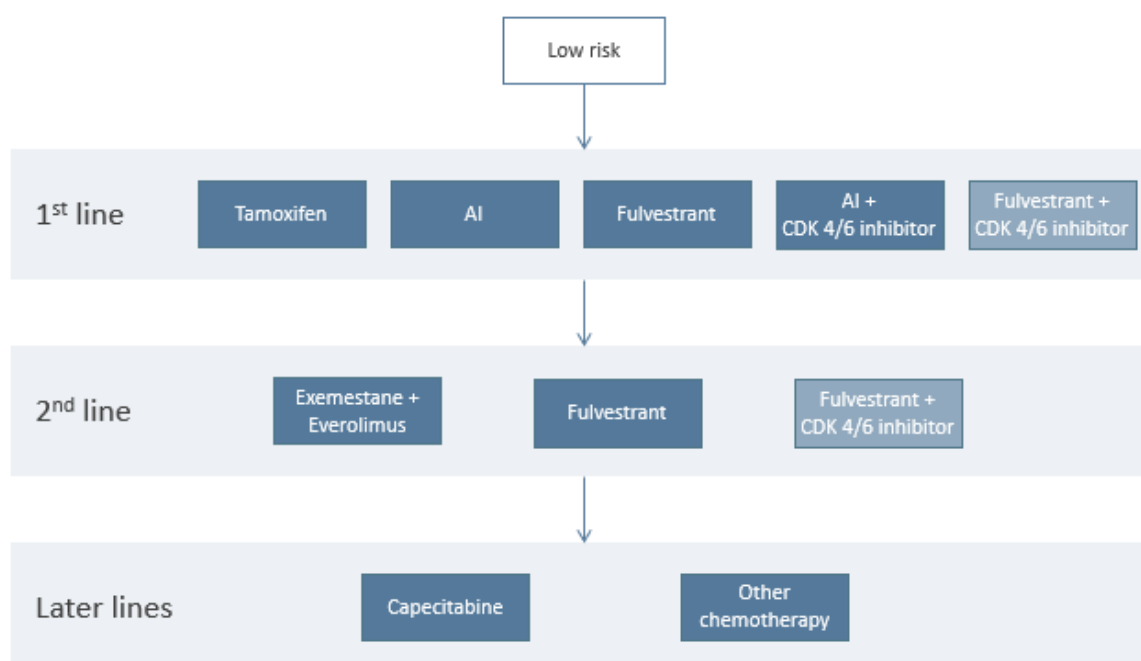
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Breast cancer is the most common cancer in women and the second most common cancer globally¹. The mainstay treatment of HR+, HER2- ABC is endocrine therapy such as tamoxifen and NSAIs, either alone or in combination with CDK4/6 inhibitors. The role of endocrine therapy includes prolonging life, managing symptoms and improving quality of life. Treatment with endocrine therapy is continued until there is evidence of disease progression or intolerability due to toxicity (Carson 2019).¹ However, endocrine therapy resistance leading to disease progression eventually occurs in many patients, representing a significant issue for optimal clinical management.
- 4.2 The target population considered in the submission is non-premenopausal patients with HR+, HER2- ABC. The ESC noted that the population in the submission included locally advanced or metastatic breast cancer (stage III or IV), however, most patients with stage III disease will not develop metastatic breast cancer. In the clinical evidence presented, patients included in the studies with stage III breast cancer had unresectable disease following chemotherapy.
- 4.3 Within this population, the submission targeted the subgroup of patients who would be suited for monotherapy rather than combination therapy with the CDK4/6 inhibitors (first-line) and for patients following progression in the first-line setting (second-line). The submission expected that fulvestrant would mostly be used in the second line setting, with a small number of patients prescribed fulvestrant in the first-line setting, predominantly in patients who cannot tolerate CDK4/6 inhibitors. The submission assumed that patients able to tolerate CDK4/6 inhibitors would be treated with them first-line.
- 4.4 There is a place for fulvestrant in combination with CDK4/6 inhibitors and such use, while not specifically prohibited under the requested fulvestrant restriction, would be prohibited in the CDK4/6 inhibitor restrictions. The submission did not present clinical evidence to support combination use. A request for listing of a CDK4/6 (i.e. ribociclib) in combination with fulvestrant for the treatment of patients with HR+, HER2-advanced breast cancer was also considered at the July 2020 PBAC meeting.
- 4.5 The clinical treatment algorithm proposed in the submission is reasonable (Figure 1).

¹ Bray, F., et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018 Nov;68(6):394-424.

Figure 1: Proposed management of HR+, HER2- ABC



ABC, advanced breast cancer; AI: nonsteroidal aromatase inhibitor; CDK: cyclin dependent kinase inhibitor; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive

Note: Fulvestrant combination with CDK4/6 inhibitors are shaded lighter to demonstrate they are not part of the current submission.

Source: Figure 1.7, p23 of the submission

- 4.6 Fulvestrant works by down-regulating and degrading oestrogen receptors. It binds to oestrogen receptors, making them change shape so that they are unable to bind to oestrogen, thereby preventing the growth stimulatory effects of oestrogen.

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

5 Comparators

- 5.1 The submission nominated anastrozole as the main comparator for the first-line, and EVE+EXE for the second-line treatment of HR+, HER2- ABC. Although the international clinical guidelines differ on the preferred sequence of first-line and second-line therapies, the commentary considered the choice of comparators to be reasonable, given that:

- **First-line:** Anastrozole is PBS listed for the first-line treatment of HR+, HER2- ABC patients. Anastrozole and letrozole (another NSAI) are considered equivalent in terms of their efficacy and anastrozole was recommended by the PBAC on a cost-minimisation basis compared to letrozole (PBS Therapeutic Relativity Sheets AC L02). In addition, randomised controlled trial (RCT) data are available for fulvestrant and anastrozole, but not for letrozole.

- Second-line ('subsequent line'): For metastatic (Stage IV) patients who have progressed on first-line endocrine-therapy, EVE+EXE is PBS listed and is one of the main targeted treatment options in Australia. Although chemotherapy and best supportive care are other options, the commentary considered they are generally reserved for patients with rapidly progressive visceral metastases. The ESC considered that other second and subsequent-line treatments such as tamoxifen and chemotherapy should also have been considered as comparators for some patients. The ESC noted that tamoxifen and chemotherapy (such as capecitabine) are less expensive than EVE+EXE.
- 5.2 The submission also nominated NSAI+CDK4/6 inhibitors (palbociclib, ribociclib) as potential comparators in the first-line setting, but did not present any clinical evidence comparing fulvestrant and NSAI+CDK4/6, nor an economic evaluation or financial estimates. The submission also noted that fulvestrant monotherapy is likely to be used in patients in the first-line setting for whom NSAI combination therapy with CDK4/6 inhibitors is not appropriate. The ESC considered this was not a reasonable comparator for fulvestrant monotherapy.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) in support of PBS listing of fulvestrant. BCNA reported that while the combination use with CDK4/6 inhibitors is currently the main area of need, having fulvestrant available through the PBS as a monotherapy and for other combination therapies would also be a welcome outcome. BCNA also stated that having fulvestrant available with a line-agnostic listing will enable it to be used more broadly to suit individual patient needs.
- 6.3 One consumer comment was also received from a medical oncologist, who noted that fulvestrant is used regularly overseas, and is associated with better quality of life than chemotherapy. Without PBS access to fulvestrant, patients may be treated with chemotherapy earlier in their treatment.

Clinical trials (first-line)

- 6.4 The submission was based on two head-to-head RCTs in the first-line setting:
- FALCON (n=462) was a randomised, double-blind, phase III trial of fulvestrant compared with anastrozole for postmenopausal women with HR+, HER2- ABC who had not previously received hormone treatment.

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- FIRST (n=205) was an open-label, phase II trial for postmenopausal women with HR+ locally advanced or metastatic disease.

6.5 Details of the trials are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
FALCON NCT01602380	A randomised, double-blind, parallel-group, multicentre, phase III study to compare the efficacy and tolerability of fulvestrant (faslodex) 500 mg with anastrozole (arimidex) 1 mg as hormonal treatment for postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not previously been treated with any hormonal therapy.	05 August 2016
	Noguchi, S., Ellis, M. J., Robertson, J. F. R., et al. Progression free survival results in postmenopausal Asian women: subgroup analysis from a phase III randomised trial of fulvestrant 500 mg vs anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON).	Breast Cancer 2018; 25; 356-364.
	Robertson, J. F. R., Bondarenko, I. M., Trishkina, E., et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial.	Lancet 2016; 388; 2997-3005.
	Robertson, J. F. R., Cheung, K. L., Noguchi, S., et al. Health-related quality of life from the FALCON phase III randomised trial of fulvestrant 500 mg versus anastrozole for hormone receptor-positive advanced breast cancer.	European Journal of Cancer 2018; 94; 206-215.
FIRST NCT00274469	A randomised, open-label, parallel-group, multicentre, phase II study to compare the efficacy and tolerability of fulvestrant (faslodex™) 500 mg with anastrozole (arimidex™) 1 mg as first-line hormonal treatment for postmenopausal women with hormone receptor positive advanced breast cancer.	19 June 2008
	Ellis, M. J., Llombart, A., Rolski, J., et al. A comparison of high-dose (HD, 500 mg) fulvestrant vs anastrozole (1 mg) as first-line treatments for advanced breast cancer: Results from FIRST.	Cancer Research. Conference: 31st Annual San Antonio Breast Cancer Symposium. San Antonio; TX United States. Sponsor: UT Health Science Centre San Antonio School of Medicine; American Association for Cancer Research; Baylor College of Medicine. Conference Publication 2009; 69.
	Robertson, J. F., Lindemann, J. P., Llombart-Cussac, A., et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomised 'FIRST' study.	Breast Cancer Research & Treatment 2012; 136; 503-11.
	Robertson, J. F., Llombart-Cussac, A., Rolski, J., et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study.	Journal of Clinical Oncology 2009; 27; 4530-5.

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CS= clinical study report; ER= Oestrogen receptor; HER2-= human epidermal growth factor receptor-2 negative; HR+= hormone receptor-positive; mg= milligrams

Source: Compiled during the evaluation based on Table 2.3, pp37-38 of the submission

6.6 The key features of the direct randomised trials in the first-line treatment setting are summarised in Table 3.

Table 3: Key features of the included evidence in first-line setting

Trial	N	Design/ duration of follow-up (median) (months)	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
FALCON	Fulvestrant 500mg: 230 Anastrozole: 232	R, DB Fulvestrant 500mg: 13.82 (0-36.8) Anastrozole: 13.24 (0-36.0)	Low	Treatment naïve	PFS, OS, CBR	Used for PFS, OS and safety
FIRST	Fulvestrant 500mg: 102 Anastrozole: 103	R, OL Fulvestrant 500mg: NR Anastrozole: NR	High	Treatment naïve in the locally advanced or metastatic setting ^a	TTP, OS, CBR	Used for PFS, OS (base case: treatment naïve subgroup) ^b

CBR: Clinical Benefit Rate, DB: Double blind, OS: Overall survival, PFS: Progression free survival, R: Randomised, TTP: time to progression
^a FIRST also recruited patients who had received previous endocrine therapy for early disease completed more than 12 months before randomisation.

^b In the model base case, the PFS and OS data from FIRST was based on a subgroup who were treatment naïve to endocrine therapy.

Source: Compiled during the evaluation based on Table 13, p69 of the FALCON CSR, Table 4, p17 of the FIRST CSR addendum, Tables 2.4, 2.5, 2.8, pp39-51 of the submission

6.7 The overall risk of bias was low in FALCON. The risk of bias was high in FIRST because it was open-label.

6.8 The patient characteristics differed between the trials and the proposed PBS population in the following important aspects:

- The proposed PBS restriction is for HER2- patients. While FALCON only enrolled HER2- patients, FIRST included patients with HER2+ (18.6%) and unknown HER2 status (34.3%), alongside HER2- (47.1%). This may reduce the applicability of the results from FIRST and the pooled results from both trials. The Pre-Sub-Committee Response (PSCR) argued that the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial (Dowsett 2008) has previously shown that HER2 status does not affect the relative difference in time to recurrence between tamoxifen and anastrozole. The ESC considered that the claim that HER2 status would not impact treatment effect was inadequately supported. The ESC noted that in clinical practice, HER2+ patients would receive HER2-directed therapies. The ESC considered HER2 status is likely to be a strong predictor of effect and the differences between the FALCON and FIRST trials may be the result of this difference in the patient populations.

- In the Australian setting approximately one third of patients with metastatic breast cancer present with de novo metastatic disease². The remainder of patients are likely to have been treated with hormonal therapy in the early disease setting. Whilst previous hormonal therapy in the early disease setting was permitted in the FIRST study, this was not allowed in the larger FALCON study. Therefore, the submission provided very little clinical evidence for most patients who would be eligible for fulvestrant in Australia.
 - The PBAC noted that patients with visceral disease are less likely to be treated with fulvestrant (or any endocrine treatment) and more likely to be treated with chemotherapy, but these patients were included in both FALCON and FIRST trials.
- 6.9 The submission did not discuss the impact of subsequent lines of treatment on OS in either trial. In FALCON the proportion of patients receiving subsequent lines of treatment were balanced between treatment arms and the comparative OS was unlikely to be biased. However, in FIRST, 5% and 10% of patients received subsequent lines of treatment in the fulvestrant and anastrozole arms, respectively (Table 22, p87 FIRST CSR). The CSR noted that the data were immature at the time of reporting and did not warrant full analysis. Thus, there is the potential for imbalance in subsequent treatments in FIRST, and hence the potential for bias in OS.

Comparative effectiveness (first-line)

- 6.10 Results based on a fixed-effects meta-analysis of PFS and OS from FALCON and FIRST are presented in Table 4.
- 6.11 Corresponding Kaplan-Meier plots are shown in Figures 2 to 4. The submission stated that the Kaplan-Meier OS plot for FALCON was not available due to immature OS data.
- 6.12 In the pooled analysis, the submission used the statistically significant OS hazard ratio from FIRST 0.70 (95% confidence interval (CI): 0.50, 0.98), which was not adjusted for baseline characteristics. In addition to the pre-specified primary analysis using a log-rank test, the submission also presented a non-significant and higher hazard ratio of 0.76, (95% CI: 0.54, 1.08), $p=0.126$, which was adjusted for baseline characteristics in a Cox proportional hazards model. The commentary, ESC and PBAC considered that it would be more appropriate to use the adjusted hazard ratio.

² No published data for Australian clinical practice were identified, however rates are likely to be similar to those in the UK as reported in Twelves et al. (2020) Systemic treatment of hormone receptor positive, human epidermal growth factor 2 negative metastatic breast cancer: retrospective analysis from Leeds Cancer Centre. BMC Cancer 20, Article number: 53 (2020).

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Table 4: Results of PFS and OS for FALCON and FIRST

Trial ID	Fulvestrant		Anastrozole		Difference in median, months	P value (log-rank test)	Hazard ratio (95% CI)
	n/N (%)	Median time to event, months (95% CI)	n/N (%)	Median time to event, months (95% CI)			
PFS*							
FALCON (PFS)	143/230 (62.2)	16.6 (13.83, 20.99)	166/232 (71.6)	13.8 (11.99, 16.59)	2.8	0.0486	0.797 (0.637, 0.999)
FIRST (TTP)	63/102 (61.8)	23.4 (NR)	79/103 (76.7)	13.1 (NR)	10.3	0.01	0.66 (0.47, 0.92)
Pooled HR (95% CI)						0.75 (0.62, 0.91)	
OS							
FALCON	67/230 (29.1)	NE	75/232 (32.3)	NE	NE	0.4277	0.875 (0.629, 1.217)
FIRST	63/102 (61.8)	54.1 (NR)	74/103 (71.8)	48.4 (NR)	5.7	0.041	0.70 (0.50, 0.98)
						0.126 (Cox proportional hazards model (adjusted))	0.76 (0.54, 1.08) (Cox proportional hazards model (adjusted))
Pooled OS HR (95% CI) (submission base case)						0.78 (0.62, 0.99)	
Pooled OS HR (adjusted in FIRST)						0.82 (0.646, 1.042, p= 0.10)	

CI = confidence interval; n = number of participants reporting data; N = total participants in group; NE = not evaluable due to insufficient data; OS: overall survival; PFS= progression free survival; TTP = time to progression

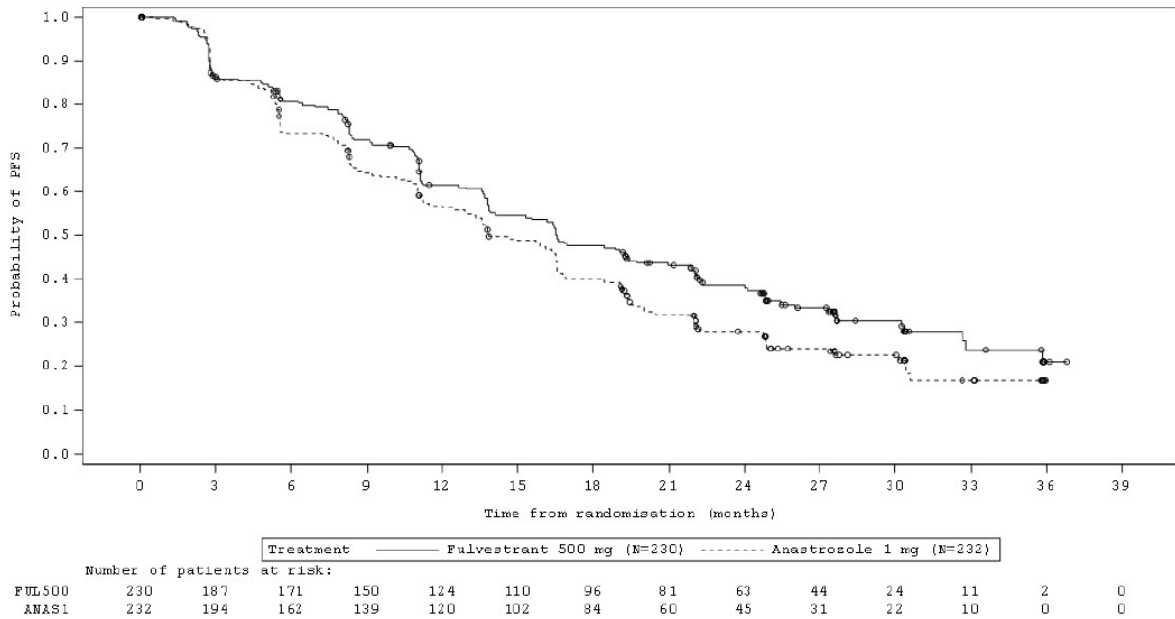
* FIRST adopted TTP instead of PFS. However, the submission considered TTP and PFS to have a similar meaning.

Note: Adjusted results based on Cox proportional hazards model as well as meta-analysed OS (stratified HR) were added during the evaluation.

Bold indicates statistically significant results

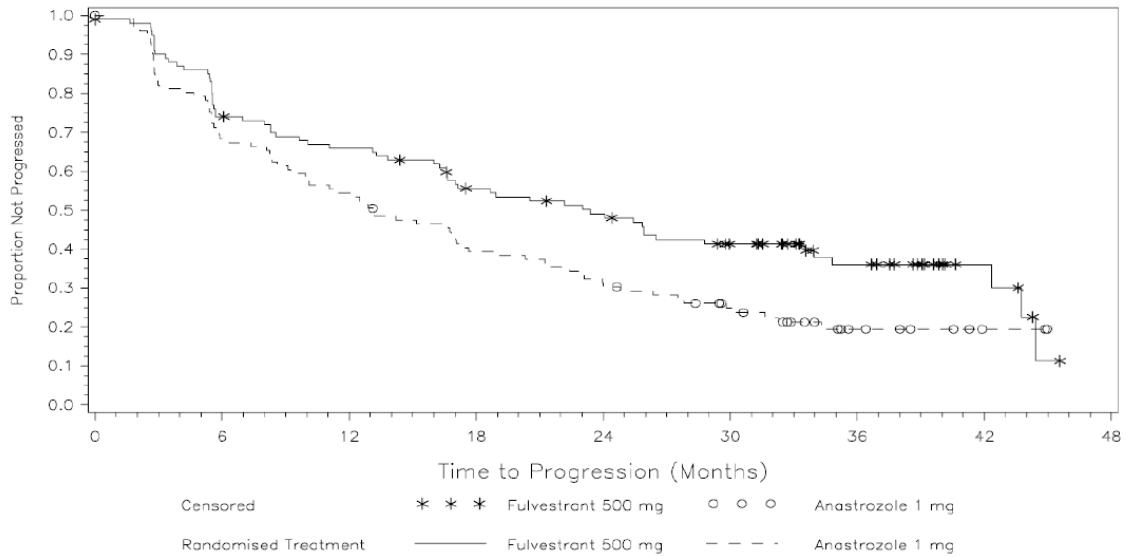
Source: Compiled during the evaluation based on Tables 2.11-2.12,2.54, pp54,56,119 of the submission

Figure 2: FALCON trial Kaplan-Meier plot of PFS (ITT analysis)



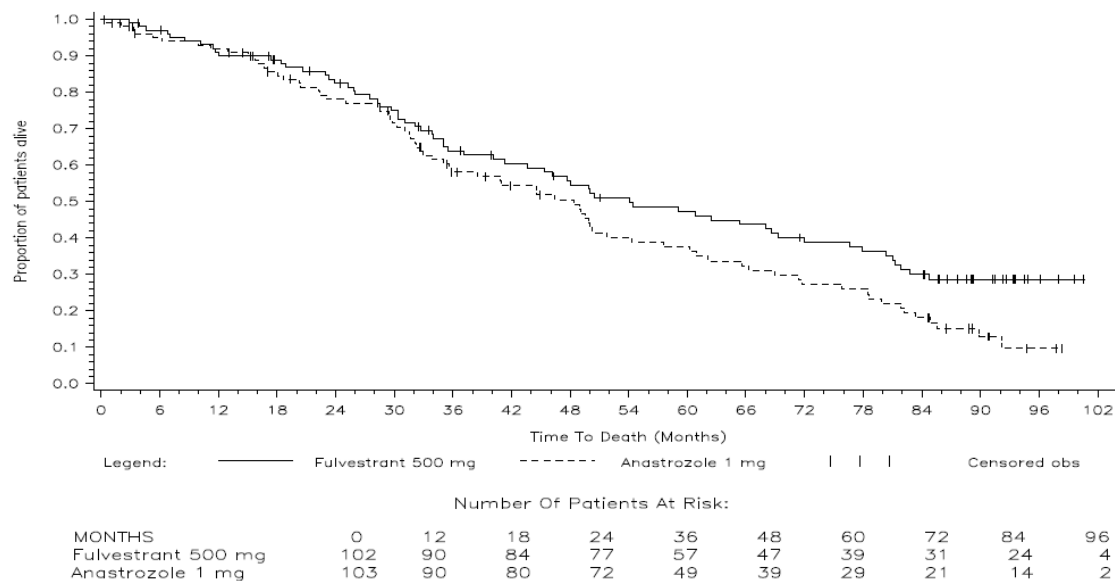
ITT = intention-to-treat; PFS = progression free survival
 Source: Figure 2.2, p55 of the submission

Figure 3: FIRST trial Kaplan-Meier plot of TTP (FAS analysis)



FAS = full analysis set; TTP = time to progression
 Source: Figure 2.3, p56 of the submission

Figure 4: FIRST trial Kaplan-Meier plot of OS (FAS analysis)



FAS = full analysis set; PFS = overall survival

Source: Figure 2.4, p57 of the submission

- 6.13 TTP was reported in FIRST instead of PFS. The definition of TTP in FIRST was similar to the definition of PFS in FALCON and thus the two outcomes were comparable.
- 6.14 The pooled OS hazard ratio (HR: 0.78; 95% CI: 0.62, 0.99) used as the basis of the clinical claim suggested that fulvestrant was superior over anastrozole. However, using the adjusted hazard ratio from FIRST, the meta-analysed hazard ratio is higher and not statistically significant ($p=0.10$): 0.820 (95% CI: 0.646, 1.042).
- 6.15 Overall, the commentary and the ESC considered that it may be inappropriate to combine the results of FALCON and FIRST for the following reasons:
- Most (53%) patients in FIRST were either HER2+ or HER2 unknown status, and so a large proportion of patients were not relevant to the target HER2- population.
 - 25% of patients in FIRST had received prior endocrine therapies for early disease, while FALCON excluded such patients. While prior endocrine usage in patients would be allowed under the proposed restriction, the base case of the economic model used data from the subgroup of patients in FIRST who had no prior endocrine therapy (along with the ITT population of FALCON) to align with proposed use in the UK setting, given that the economic evaluation model was originally developed for NICE. Subgroup results for OS from FIRST (which inform the base case of the model) are presented in Table 5.

Table 5: OS hazard ratios for the subgroup analysis conducted in FIRST patients based on prior endocrine treatment for early disease

Prior endocrine therapy status	N	HR (95% CI)
Without prior endocrine therapy ^a	153/205 = 74.60%	0.63 (95% CI: 0.42, 0.93)
With prior endocrine therapy	52/205 = 25.4%	1.01 (95% CI: 0.51, 1.99)
Full analysis set	205	0.70 (95% CI: 0.50, 0.98)

CI: Confidence interval, HR: Hazard ratio

Source: Compiled during the evaluation based on section 2A.7; p18, FIRST CSR Addendum 3

^a Data from this subgroup (along with data from FALCON) were used in the base case of the economic model.

6.16 The PSCR stated that the presence of visceral disease was a treatment effect modifier both in FALCON and FIRST, with subgroup analyses showing a greater relative treatment effect in patients with non-visceral disease (e.g. the HR for PFS in FALCON was 0.59 (95% CI: 0.42, 0.84) in patients with non-visceral disease compared with 0.99 (95% CI: 0.74, 1.33) in the visceral disease subgroup). The PSCR further stated that patients with visceral disease are more likely to be treated with chemotherapy rather than endocrine therapy and therefore, the relative treatment effect of fulvestrant in the patient group for which it would be used in Australian clinical practice (i.e. non-visceral disease) is greater than the overall trial population results.

Comparative harms (first-line)

6.17 A summary of adverse events (AEs) in FALCON and FIRST is provided in Table 6. The submission stated that the incidences of AEs were generally comparable between treatment arms in FALCON and FIRST.

Table 6: Overview of adverse events from the FALCON and FIRST studies

	FALCON		FIRST	
	Fulvestrant N=228 n (%)	Anastrozole N=232 n (%)	Fulvestrant N=101 n (%)	Anastrozole N=103 n (%)
Any AE	166 (72.8)	173 (74.6)	71 (70.3)	72 (69.9)
Any AE causally related to treatment	91 (39.9)	76 (32.8)	30 (29.7)	28 (27.2)
Any AE of grade 3 or higher	51 (22.4)	41 (17.7)	18 (17.8)	11 (10.7)
Any AE of grade 3 or higher, causally related to treatment	10 (4.4)	4 (1.7)	1 (1.0)	0
Any AE with an outcome of death	6 (2.6)	7 (3.0)	0	1 (1.0)
Any AE with an outcome of death, causally related to treatment	0	0	0	0
Any AE leading to discontinuation of treatment	16 (7.0)	11 (4.7)	3 (3.0)	3 (2.9)
Any SAE (including events with outcome of death)	30 (13.2)	31 (13.4)	12 (11.9)	10 (9.7)
Any SAE (including events with outcome of death), causally related to treatment	4 (1.8)	3 (1.3)	1 (1.0)	0

AE = adverse event; SAE = serious adverse event

Source: Table 2.15, p58 of the submission

6.18 The following differences in specific Grade 3 or more AEs were observed between the treatment arms in FALCON and FIRST.

- Slightly more patients in the fulvestrant arm compared with the anastrozole arm

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in FALCON reported an increase in the following specific AEs: Alanine aminotransferase (ALT, 7.0% versus 3.0%), arthralgia (16.7% versus 10.3%), back pain (9.2% versus 6.0%), fatigue (11.4% versus 6.9%) and myalgia (7.0% versus 3.4%).

- Slightly fewer patients in the fulvestrant arm in FALCON had anaemia (3.9% versus 8.6%) and hypertension (6.6% versus 9.1%).
- Slightly more patients in the fulvestrant arm compared with the anastrozole arm in FIRST reported an increase in the following specific AEs: bone pain (13.9% versus 9.7%), hypertension (6.9% versus 1.9%), nausea (10.9% versus 6.8%) and vomiting (8.9% versus 2.9%).
- Slightly fewer patients in the fulvestrant arm in FIRST experienced fatigue (1.0% vs 7.8%), headache (4.0% vs 12.6%), hot flush (7.9% vs 13.6%) and myalgia (3.0% vs 8.7%).

Benefits/harms (first-line)

6.19 A summary of the comparative benefits and harms for fulvestrant versus anastrozole is presented in the table below.

Table 7: Summary of comparative benefits and harms for fulvestrant and anastrozole

Benefits						
Progression free survival (median duration of follow up 13.2-13.8 months FALCON, not reported for FIRST)						
Event	Fulvestrant	Anastrozole	Absolute Difference	Pooled HR (95% CI)		
Progressed, n (%)				0.75 (0.62, 0.91)		
FALCON	143/230 (62.2)	166/232 (71.6)	9.4	P=0.003		
FIRST	63/102 (61.8)	79/103 (76.7)	14.9	I ² =0%		
Median PFS, months (95% CI)						
FALCON	16.6 (13.83, 20.99)	13.8 (11.99, 16.59)	2.8			
FIRST	23.4 (NR)	13.1 (NR)	10.3			
Overall survival (median duration of follow up 13.2-13.8 months FALCON, not reported for FIRST)						
Deaths, n/N (%)				0.78 (0.62, 0.99)		
FALCON	67/230 (29.1)	75/232 (32.3)	3.2	P= 0.04		
FIRST	63/102 (61.8)	74/103 (71.8)	10.0	I ² =0%		
Patients event free (%)						
FIRST, 12 months	91%	92%	1%			
FIRST, 24 months	83%	78%	5%			
FIRST, 48 months	56%	51%	5%			
FIRST, 72 months	39%	27%	12%			
Median OS, months (95% CI)						
FALCON	NE	NE				
FIRST	51.1 (NR)	48.4 (NR)	5.7			
Harms						
	Fulvestrant n/N	Anastrozole n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Fulvestrant	Anastrozole	
Any AE grade 3 or higher						
FALCON	51/228 (22.4)	41/232 (17.7)	1.34 (0.93, 1.93)	22	18	4.7 (-2.63, 12.0)
FIRST	18/101 (17.8)	11/103 (10.7)	1.67 (0.83, 3.35)	18	11	7.1 (-2.61, 16.86)

Source: Tables 2.17-2.18 and figures 2.5-2.6, attachment 2.2 of the submission

HR = hazard ratio; NE = not evaluable; RD = risk difference; RR = risk ratio

* Median duration of follow-up: FALCON = 13.2 (fulvestrant arm), 13.8 months (anastrozole arm); FIRST = 8 months (fulvestrant arm), 6.5 months (anastrozole arm)

- 6.20 On the basis of the evidence presented by the submission, for every 100 patients treated with fulvestrant in comparison with anastrozole:
- Approximately 9 additional patients will remain progression-free after 13 months, based on the FALCON trial.
 - No statistically significant difference in AEs grade 3 or higher was shown for fulvestrant compared with anastrozole.

Clinical claim (first-line)

- 6.21 The submission described fulvestrant as superior in terms of effectiveness compared with anastrozole for the first-line treatment setting for patients with (unresectable) Stage III and IV breast cancer. The commentary considered this may be plausible, given that:
- The PFS HR for both FALCON and FIRST was statistically significant: 0.797 (95% CI: 0.637, 0.999) and 0.66 (95% CI: 0.47, 0.92) respectively. It was also statistically significant when pooled over the two trials: 0.75 (95% CI: 0.62, 0.91).
 - The OS HR pooled from FALCON and FIRST was statistically significant: 0.78 (95% CI: 0.62, 0.99).
- 6.22 However, the ESC considered that the clinical claim was not well-supported because:
- the FIRST study included patients with HER2 positive breast cancer and therefore was not representative of the population requested for listing; and
 - the FALCON study excluded patients who had prior endocrine therapy and therefore was only applicable to patients with de novo advanced or metastatic disease.
 - The FALCON trial was most representative of the requested population, however the OS data were immature, with 69% of patients still alive at the data cut and the OS hazard ratio was not statistically significant, 0.875 (95% CI: 0.629, 1.217).
- 6.23 The ESC considered that the results of the FALCON trial were most relevant to the requested population, however noted that more mature data will not be available until 2022. The pre-PBAC response argued that the FIRST trial was also applicable, noting that it included patients with prior endocrine therapy (completed more than 12 months prior to enrolment) for early disease.
- 6.24 The submission described fulvestrant as non-inferior in terms of safety compared with anastrozole for the first-line treatment setting. The incidences of overall adverse events and individual adverse events of Grade 3 or higher were generally slightly higher in the fulvestrant arm compared to the comparator.
- 6.25 The PBAC considered that the claim of superior comparative effectiveness was reasonable, however the magnitude of benefit could not be reliably estimated given

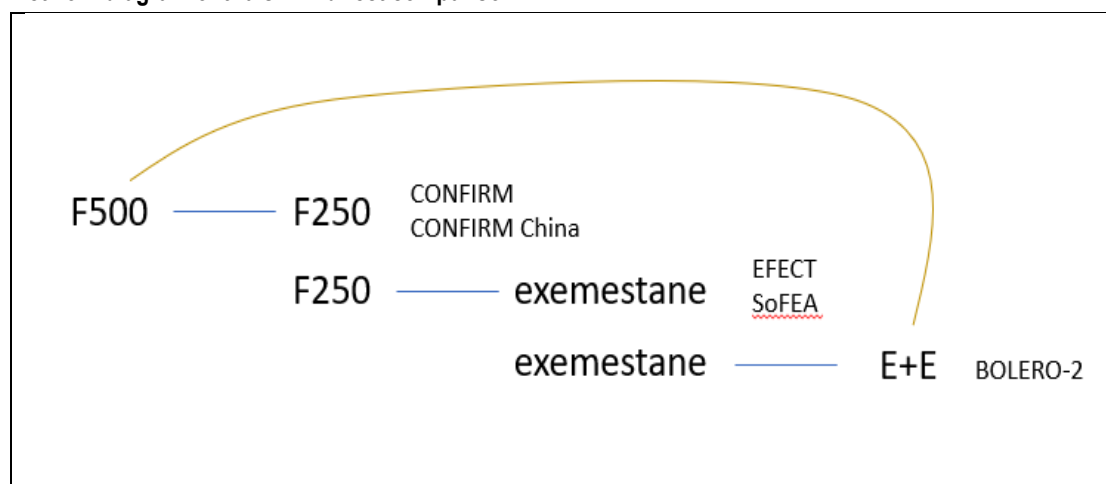
the limited applicability of the trials, the risk of bias in the FIRST trial (due to the open-label design) and the immaturity of the FALCON trial.

- 6.26 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Clinical trials (second-line)

- 6.27 No head-to-head RCTs comparing fulvestrant to EVE+EXE for the second-line treatment of HR+, HER2- ABC were identified. The submission based its clinical claim on an “informal indirect comparison” approach to link evidence based on five RCTs in the second-line setting (as shown in figure 5). The “informal indirect comparison” was not a statistical analysis of the comparative effectiveness of fulvestrant versus EVE+EXE. Instead, it was simply a restatement of the results of the underlying trials and the meta-analyses of trials.
- 6.28 A formal two-step indirect comparison via separate Bucher single pairwise indirect comparisons was presented as an attachment to the submission. The submission noted that, due to key differences in the study populations across the trials, the formal comparison had significant limitations.

Figure 5: Network diagram of trials in indirect comparison



F500= Fulvestrant 500mg; F250 = Fulvestrant 250mg; E+E = Everolimus + Exemestane
 Source: Figure 2.9, p80 of the submission

- 6.29 Trials included in the analysis were:
- CONFIRM (n=736) was a randomised, double-blind, phase III, parallel-group, multicentre study comparing the efficacy and tolerability of fulvestrant 500mg versus fulvestrant 250mg in postmenopausal women with HR+ ABC progressing or relapsing after previous endocrine therapy.
 - CONFIRM China (n=221) was a randomised, double-blind, phase III, parallel-group, multicentre study comparing the efficacy and tolerability of fulvestrant

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500mg versus fulvestrant 250 mg in postmenopausal women with HR+ ABC progressing or relapsing after previous endocrine therapy.

- EFECT (n=693) was a randomised, double-blind, phase III, multicentre study to compare the efficacy and tolerability of fulvestrant 250 versus exemestane in postmenopausal women with HR+ ABC with disease progression after prior NSAI therapy.
- SoFEA (n=480) was a partially-blind, phase III, randomised trial of fulvestrant 250mg with or without concomitant anastrozole compared with exemestane in postmenopausal women with HR+ ABC following progression on NSAIs.
- BOLERO-2 (n=724) was a randomised double-blind, phase III, placebo-controlled study of EVE+EXE compared with placebo plus exemestane in the treatment of postmenopausal women with HR+ ABC who are resistant to letrozole or anastrozole.

6.30 Details of the trial publications are provided in Table 8.

Table 8: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CONFIRM NCT00099437	A randomised, double-blind, parallel-group, multicentre, phase III study comparing the efficacy and tolerability of fulvestrant (faslodex™) 500 mg with fulvestrant (faslodex™) 250 mg in postmenopausal women with oestrogen receptor-positive advanced breast cancer progressing or relapsing after previous endocrine therapy.	09 July 2009
	Di Leo, A., Jerusalem, G., Petruzelka, L., et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer.	Journal of Clinical Oncology 2010; 28; 4594-600.
	Di Leo, A., Jerusalem, G., Petruzelka, L., et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomised CONFIRM trial.	Journal of the National Cancer Institute 2014; 106; djt337.
	Di Leo, A., Jerusalem, G., Torres, R., et al. 2018. First-line vs second-line fulvestrant for hormone receptor-positive advanced breast cancer: A posthoc analysis of the CONFIRM study.	Breast 2018; 38; 144-149.
CONFIRM (China) NCT01300351	A randomised, double-blind, parallel-group, multicentre study comparing the efficacy and tolerability of fulvestrant 500 mg versus 250 mg in postmenopausal women with er+ advanced breast cancer progressing or relapsing after previous endocrine therapy.	20 August 2014
	Zhang, Q., Shao, Z., Shen, K., et al. Fulvestrant 500 mg vs 250 mg in postmenopausal women with oestrogen receptor-positive advanced breast cancer: a randomised, double-blind registrational trial in China.	Oncotarget 2016; 7; 57301-57309.
EFECT NCT00065325	A randomised, double-blind, multicentre study to compare the efficacy and tolerability of fulvestrant (faslodex™) vs exemestane (aromasin™) in postmenopausal women with hormone receptor positive advanced breast cancer with disease progression after prior nonsteroidal aromatase inhibitor (AI) therapy.	19 December 2006

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Trial ID	Protocol title/ Publication title	Publication citation
	Chia, S., Gradishar, W., Mauriac, L., et al. Double-blind, randomised placebo-controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT.	Journal of Clinical Oncology 2008; 26; 1664-70
	Mauriac, L., Romieu, G. & Bines, J. 2009. Activity of fulvestrant versus exemestane in advanced breast cancer patients with or without visceral metastases: data from the EFECT trial.	Breast Cancer Research & Treatment 2009; 117; 69-75.
SoFEA NCT00253422	No CSR available A partially-blind phase III randomised trial of fulvestrant (faslodex™) with or without concomitant anastrozole (arimidex™) compared with exemestane in postmenopausal women with er+ve locally advanced/metastatic breast cancer following progression on nonsteroidal aromatase inhibitors.	Date not provided
	Johnston, S. R., Kilburn, L. S., Ellis, P., et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on nonsteroidal aromatase inhibitors in postmenopausal patients with hormone receptor positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncology, 14, 989-98.	Lancet Oncology 2013; 14; 989-98
BOLERO-2 (NCT00863655)	A randomised double-blind, placebo-controlled study of everolimus in combination with exemestane in the treatment of postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole.	Date not provided
	Campone, M., Bachelot, T., Gnant, M., et al. Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: subgroup analysis from the BOLERO-2 study.	Eur J Cancer 2013; 49; 2621-32.
	Ito, Y., Masuda, N., Iwata, H., et al. Everolimus plus exemestane in postmenopausal patients with oestrogen-receptor-positive advanced breast cancer - Japanese subgroup analysis of BOLERO-2.	Gan To Kagaku Ryoho 2015; 42; 67-75.
	Noguchi, S., Masuda, N., Iwata, H., et al. Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone receptor positive breast cancer in BOLERO-2.	Breast Cancer 2014; 21; 703-14.
	Piccart, M., Hortobagyi, G. N., Campone, M., et al. Everolimus plus exemestane for hormone receptor positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2.	Ann Oncol 2014; 25; 2357-62.
	Pritchard, K. I., Burris, H. A., 3rd, Ito, Y., et al. Safety and efficacy of everolimus with exemestane vs exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2.	Clin Breast Cancer 2013; 13; 421-432.e8.

CS= clinical study report; ER= oestrogen receptor; HER2-= human epidermal growth factor receptor-2 negative; HR+= hormone receptor-positive; mg= milligrams

Source: Compiled during the evaluation based on Tables 2.25- 2.26, pp75-78 of the submission.

- 6.31 Table 9 summarises the key features of the relevant trials used in the second-line setting.
- 6.32 CONFIRM had a low overall risk of bias. However, the risk of bias was uncertain in CONFIRM China, EFECT and BOLERO-2. The overall risk of bias was high in SoFEA, primarily because the trial was open-label and because the CSR was not available.

Table 9: Key features of the trials in the second-line setting

Trial	Treatments: N	Design/ duration of follow-up (median) (months)	Risk of bias	Patient population	Outcome(s)
CONFIRM	Fulvestrant 500mg: 362 Fulvestrant 250mg: 374	R, DB NR	Low	Endocrine-sensitive, endocrine-resistant	PFS, OS
CONFIRM China	Fulvestrant 500mg: 362 Fulvestrant 250mg: 374	R, DB NR	Uncertain	Endocrine-sensitive, endocrine-resistant	PFS
EFFECT	Fulvestrant 250mg: 351 Exemestane: 342	R, DB Fulvestrant 250mg: 3.55 (0-21.85) Exemestane: 3.55 (0-25.72)	Uncertain	Relapsed or progressed on an NSAID	TTP, OS
SoFEA	Fulvestrant 250mg:231 Exemestane: 249	R, OL 37.9 (IQR:23.1-50.8) across both arms	High	Relapsed or progressed on an NSAID	PFS, OS
BOLERO-2	everolimus + exemestane: 485 Placebo+Exemestane: 239	R, DB 18 across both arms	Uncertain	Resistant to first-line AI monotherapy	PFS, OS

DB: Double blind; NR: Not reported, NSAID: Non-steroidal aromatase inhibitor, OL: Open Label, OS: Overall survival, PFS: Progression free survival, R: Randomised, TTP: Time to progression

Source: Compiled during the evaluation based on, Tables 2.28, 2.34, pp82-93 of the submission

6.33 The patient characteristics differed between the trials and the proposed PBS population in the following important aspects, which could both violate the exchangeability assumption:

- The proposed PBS restriction specified that patients must be HER2-. Only BOLERO-2 was confirmed to include only HER2- patients. The HER2 status of the other trials was not reported.
- CONFIRM, CONFIRM China, EFFECT, SoFEA and BOLERO-2 differed based on the number of prior endocrine therapies. In BOLERO-2 (EVE+EVE vs EXE) more than 50% of patients had two or more prior hormonal therapies, while in CONFIRM (fulvestrant 500 vs 250mg) 12-15% of patients had two prior endocrine therapies and only one prior hormonal therapy in the advanced disease setting was permitted.

Comparative effectiveness (second-line)

6.34 Table 10 presents the results of PFS and OS for CONFIRM, CONFIRM China, EFFECT, SoFEA and BOLERO-2 in the second-line setting. It also contains pooled PFS and OS results based on fixed-effects meta-analyses of CONFIRM and CONFIRM China, and separately EFFECT and SoFEA.

Table 10: Results of PFS and OS across the studies

Comparison	Intervention		Comparator		Difference in median	P value (log-rank test)	Hazard ratio (95% CI)
	n/N (%) progressed	Median time to event, months (95% CI)	n/N (%) progressed	Median time to event, months (95% CI)			
PFS							
FULV500 vs FULV250	FULV500		FULV250				
CONFIRM	297/362 (82.0)	6.5 (NR)	321/374 (85.8)	5.5 (NR)	1.0	0.006	0.80 (0.68, 0.94)
CONFIRM China	76/111 (68.47)	8.0	76/110 (69.10)	4.0	4.0	0.078	0.75 (0.54, 1.03)
Pooled CONFIRM and CONFIRM China						0.002	0.79 (0.68, 0.91)
FULV250 vs EXE	FULV250		EXE 25mg				
EFFECT	288/ (82.1)	3.68 (NR) ^a	299/ (87.4)	3.68 (NR) ^a	0	0.653	0.96 (0.82, 1.13)
SoFEA	221/231	4.8 (3.6, 5.5)	233/249	3.4 (3.0, 4.6)	1.4	0.56	0.95 (0.79, 1.14)
Pooled EFFECT and SoFEA						0.48	0.96 (0.85, 1.08)
EVE+EXE vs EXE	EVE 10mg + EXE 25mg		EXE 25mg				
BOLERO-2	310/485 (63.9)	7.82 (6.93, 8.48)	200/239 (83.7)	3.19 (2.76, 4.14)	4.63	<0.0001	0.45 (0.38, 0.54)
OS							
FULV500 vs FULV250	FULV500		FULV250				
CONFIRM	261/362 (72.1)	26.4	293/374 (78.3)	22.3	4.1	0.02	0.81 (0.69, 0.96)
CONFIRM China	NR	NR	NR	NR	NR	NR	NR
FULV250 vs EXE	FULV250		EXE 25mg				
EFFECT ^b	209/351 (59.5)	24.35	197/342 (57.9)	23.10	1.25	0.9072	1.012 (0.833, 1.229)
SoFEA	167/231 (72%)	19.4 (16.8, 22.8)	173/249 (69%)	21.6 (19.4, 23.9)	2.2 favouring EXE	0.68	1.05 (0.84, 1.29)
Pooled EFFECT and SoFEA						0.71	1.03 (0.89, 1.19)
EVE+EXE vs EXE	EVE + EXE		EXE 25mg				
BOLERO-2	267/485 (55.1)	31.0 (28.0, 34.6)	143/239 (59.8)	26.6 (22.6, 33.1)	4.4	0.14	0.89 (0.73, 1.10)

CI = confidence interval; EVE= Everolimus; EXE= Exemestane; NR = not reported; n = number of participants reporting data; N = total participants in group; PFS = progression free survival; TPP = time to progression

a = Overall survival was not an outcome analysed in the CONFIRM China trial.

b = median time to death was calculated on the assumption one month is equal to 30.4375 days

FULV250 represents fulvestrant 250mg and FULV500 represents fulvestrant 500mg

Bold indicates statistically significant results

Source: Compiled during evaluation using Tables 2.36-2.37,2.57, pp96,101,125 of the submission

6.35 An adjusted indirect comparison was presented as an attachment to the submission, and comprised two steps:

- Step 1: Fulvestrant 500 mg versus EXE via fulvestrant 250 mg as the common comparator

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- Step 2: Results of Step 1 versus EVE+EXE via EXE as the common comparator.

Table 11: Summary of progression free survival and overall survival results of the adjusted indirect comparison

Trial ID	Proposed medicine versus common reference Hazard ratio (95% CI)	Comparator versus common reference Hazard ratio (95% CI)	Indirect comparison Hazard ratio (95% CI)	p-value
PFS				
Step 1: Fulvestrant 500 mg vs exemestane with fulvestrant 250 mg as common comparator				
	0.79 (0.68, 0.91)	1.04 (0.92, 1.18)	0.76 (0.63, 0.91)	0.004
Step 2: Step 1 vs Eve+Exe with exemestane as common comparator				
	0.76 (0.63, 0.91)	0.45 (0.38, 0.54)	1.685 (1.302, 2.181)	0.0001
OS				
Step 1: Fulvestrant 500 mg vs exemestane with fulvestrant 250 mg as common comparator				
	0.81 (0.69, 0.96)	0.97 (0.84, 1.12)	0.834 (0.67, 1.04)	0.1064
Step 2: Step 1 vs Eve+Exe with exemestane as common comparator				
	0.834 (0.67, 1.04)	0.89 (0.73, 1.1)	0.94 (0.69, 1.27)	0.6735

CI = confidence interval; n = number of participants reporting data; N = total participants in group; OS: Overall survival; PFS: progression free survival

Source: Compiled during the evaluation based on Tables 2.31-2.32 of attachment A2.5_formal_ITC_vs_Eve+Exe

- 6.36 PFS was estimated to be statistically significantly worse with fulvestrant compared to EVE+EXE: PFS hazard ratio: 1.69 (95% CI: 1.30, 2.18) (Table 11).
- 6.37 The adjusted indirect comparison estimated an OS hazard ratio of 0.94 (95% CI: 0.69, 1.27). The submission did not propose a non-inferiority margin. However, the commentary considered that it may not be reasonable to conclude that fulvestrant is non-inferior to EVE+EXE in terms of OS, because the upper 95% confidence limit of 1.27 represents a substantial increase in mortality, and because it does not capture the additional unquantified uncertainty inherent in all adjusted indirect comparisons, in respect of the transitivity of treatment effects across trials. The transitivity assumption is likely to be violated, given the heterogeneity between trials in terms of HER2 status and number of prior therapies and the variability in PFS and OS in the control arms of the trials.

Comparative harms (second-line)

- 6.38 A summary of key adverse events (AEs) for the fulvestrant 500mg arm in CONFIRM and the EVE+EXE arm in BOLERO-2 is provided in Table 12.

Table 12: Summary of patients who had at least 1 AE in any category

CONFIRM trial	Number (%) of patients
	Fulvestrant 500 mg N=361
Any AE	243 (67.3)
Any causally related AE	96 (26.6)
Any SAE	29 (8.0)
Any causally related SAE	1 (0.3)
Any AE leading to discontinuation of treatment (DAE)	8 (2.2)
Any causally related DAE	2 (0.6)
Any other significant AE (OAE)	0
Any AE of CTC grade 3 or higher	53 (14.7)
Any causally related AE of CTC grade 3 or higher	4 (1.1)
Any AE with outcome of death	5 (1.4)
Any causally related AE with outcome of death	0
BOLERO-2 trial	Everolimus + Exemestane (n = 482)
Any SAE	157 (32.6)
Suspected to be drug-related	63 (13.1)
Any AE of CTC grade 3 or higher	266 (55.2)
Suspected to be drug-related	197 (40.9)
Any AEs leading to treatment discontinuation (DAE)	140 (29.0)
Any AE with outcome of death	
Total	22 (4.6)
Related to disease progression	14 (2.9)
Related to adverse events	8 (1.7)
On treatment deaths ≤4 months from randomisation	
Total	11 (2.3)
Related to disease progression	6 (1.2)
Related to adverse events	5 (1.1)
On treatment deaths >4 months after randomisation	
Total	11 (2.3)
Related to disease progression	8 (1.7)
Related to adverse events	3 (0.6)

AE = adverse event; CTC: Common Terminology Criteria; DAE = adverse event leading to discontinuation of treatment; OAE = other adverse event; SAE = serious adverse event

Source: Compiled during the evaluation based on Tables 2.38,2.46, pp105, 111 of the submission

6.39 The submission presented safety outcomes of all five trials that were considered in the informal indirect comparison. However, CONFIRM included the submission’s proposed intervention (fulvestrant 500mg) and BOLERO-2 included the proposed comparator (EVE+EXE) and were therefore most relevant to the submission. The submission used an indirect comparison to claim superior safety of fulvestrant 500mg over EVE+EXE. The commentary considered this was reasonable.

6.40 Fulvestrant 500mg had substantially better safety results compared with EVE+EXE:

- Any SAE was 8% versus 33%.
- Any AE of CTC grade ≥3 or higher was 15% versus 55%.
- AE of CTC grade ≥3 or higher causally related to drug was 1% versus 41%.
- Any DAE was 1% versus 29%.
- Any AE with the outcome of death was 1% versus 5%.

Benefits/harms (second-line)

6.41 A benefits/harms analysis was not presented as the clinical claim is of non-inferiority.

Clinical claim (second-line)

6.42 Based on the informal indirect comparison, the submission stated that fulvestrant 500 mg appears superior to EVE+EXE in terms of OS. The submission acknowledged that the indirect approach had its limitations, and thus, the claim of non-inferiority of fulvestrant to EVE+EXE was made in terms of OS benefit.

6.43 The ESC considered the claim of non-inferior effectiveness was not adequately supported for the following reasons:

- The informal indirect comparison did not allow a meaningful comparison of outcomes with fulvestrant versus EVE+EXE.
- The formal adjusted indirect comparison was also limited, as the transitivity assumption is likely to be violated, given that factors such as HER2 status and prior treatments varied substantially between trials.
- The adjusted indirect comparison found that PFS was significantly worse with fulvestrant compared to EVE+EXE: PFS hazard ratio: 1.69 (95% CI: 1.30, 2.18).
- The submission did not propose a non-inferiority margin. However, it may not be reasonable to conclude that fulvestrant is non-inferior to EVE+EXE in terms of OS, because the upper 95% confidence limit of 1.27 represents a substantial increase in mortality.

6.44 The submission claimed that fulvestrant was superior in terms of safety compared with EVE+EXE.

6.45 The PBAC considered that the claim of superior comparative safety was reasonable, noting the interpretation of the safety data was difficult due to the limitations of the clinical trial data and the incomplete reporting of adverse events in the trials.

6.46 The PBAC considered that the claim of non-inferior comparative effectiveness was not well-supported by the data given the differences between the trials (e.g. in terms of HER2 status and number of prior therapies, and the variability in PFS and OS in the control arms of the trials). However, the PBAC considered that, in light of the superior comparative safety, there was likely a clinical benefit to fulvestrant in particular groups of patients.

Economic analysis (first-line)

6.47 The submission presented a cost-effectiveness model comparing fulvestrant to anastrozole as first-line treatment for HR+ HER2- ABC, based on the FALCON and FIRST trials. This is consistent with the clinical claim of superior efficacy and non-inferior

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safety. However the ESC considered that the claim of superior efficacy was not well-justified by the evidence presented.

6.48 Table 13 summarises the key components of the economic evaluation for first-line therapy.

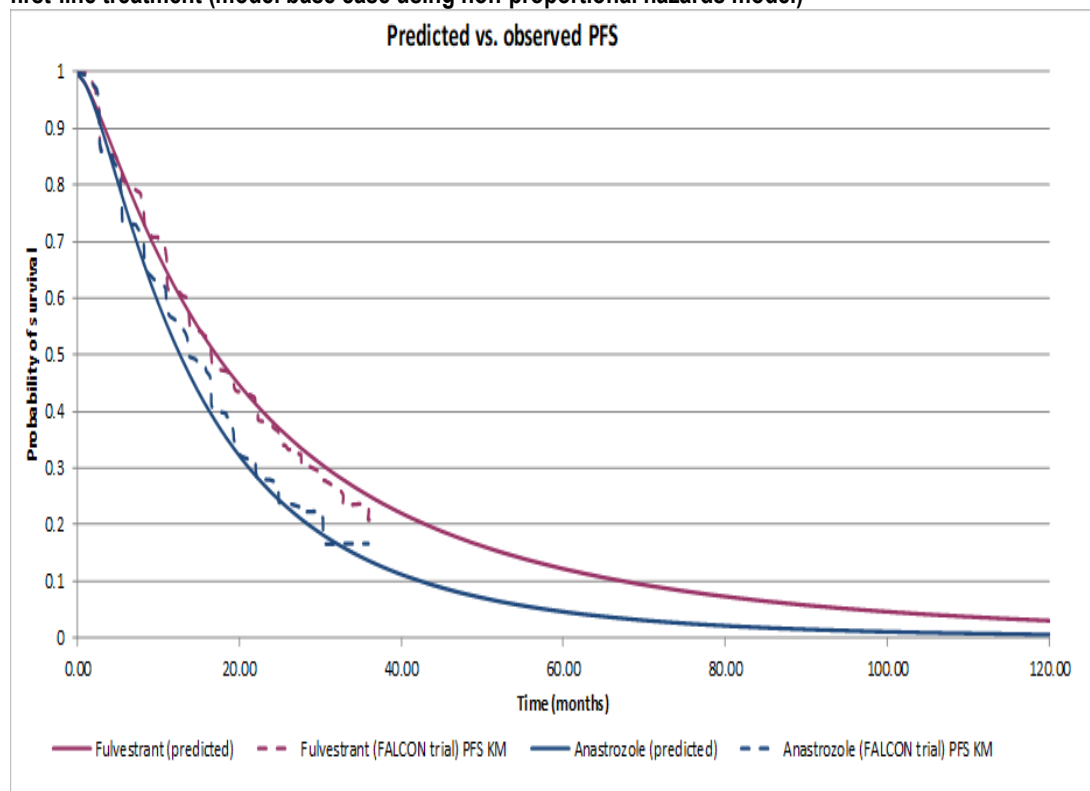
Table 13: Summary of model structure, key inputs and rationale for first-line treatment

Component	Summary	Justification/comments
Type of analysis	Cost-utility analysis.	This is reasonable, however the commentary and the ESC considered that the clinical claim of superiority was not justified well.
Outcomes	Life-years gained (and quality adjusted life-years gained (QALY).	This is appropriate.
Time horizon	10 years in the model base case 30 years in sensitivity analyses	The median follow-up time for PFS in the FALCON trial (13.82 months for fulvestrant; 13.24 for anastrozole) is short. The ICER is highly sensitive to a shorter time horizon of 5 years.
Methods used to generate results	Partitioned survival model.	This is appropriate.
Health states	Three health states: Progression free survival (PFS): - Complete response - Partial response - Stable disease Progressive disease (PPS): Death	This model structure is reasonable.
Cycle length	4 weeks	This is appropriate.
Allocation to health states	No specific transition probabilities modelled. Health state allocation over time determined by progression free and overall survival curves from the FALCON and FIRST trials	Model inputs PFS and OS were based on meta-analysis data from the FALCON and FIRST trials for the endocrine naïve population only. There were applicability issues with the FALCON and FIRST trials, as outlined in the comparative effectiveness section.
Extrapolation method	The base-case model assumed a non-proportional hazards model and used a methodology that allowed the simultaneous extrapolation and meta-analysis of Kaplan-Meier curves from FALCON and FIRST. PFS was extrapolated using the generalised gamma distribution (the second best statistical fit) and OS extrapolated using Weibull (the best statistical fit). Time to treatment discontinuation was based on the PFS from FALCON. Extrapolation was applied for the duration of the model; no observed trial data were used in the base case.	The commentary and the ESC considered that a meta-analysis using FALCON and FIRST data may not be appropriate given the issues with the FIRST trial and OS data from FALCON is immature. The ESC considered that the extrapolation likely over-predicted incremental efficacy. The ESC noted that the ICER is highly sensitive to the choice of extrapolation approach (particularly proportional hazards versus non-proportional hazards). Treatment duration should have been based on time to treatment discontinuation from both FALCON and FIRST rather than being based on PFS from FALCON.
Utilities	FALCON and Lloyd (2006) for PFS and PPS Doyle (2006), Swinburn (2010) and Boehringer Ingelheim Ltd (2014) for disutilities.	The submission did not test the use of the Australian scoring algorithm, which is also available for EQ-5D-3L. The duration of the adverse events was based on studies in NICE UK manufacturer submissions and may not reflect the Australian clinical setting.
Software package	Excel 2016	

Source: Table 3.1, Table 3.12 and Table 3.15, pp127,148-149 of the submission and CEA Model workbook.
ITT = intention to treat; OS = overall survival; PFS = progression-free survival; PPS = progressive disease.

- 6.49 In the base case analysis, a non-proportional hazards model was assumed with PFS and OS from the meta-analysis from FALCON and FIRST for fulvestrant and anastrozole modelled independently. PFS and OS for fulvestrant and anastrozole were estimated by fitting parametric survival distributions to the PFS and OS trial data from FALCON and FIRST using a methodology that allowed a simultaneous extrapolation and meta-analysis of Kaplan-Meier curves from FALCON and FIRST trials. This was achieved by relating the Kaplan-Meier curves of each of the treatments directly to the parameters of each of the parametric distributions tested. The extrapolated curves were validated by clinicians as part of the NICE 2017 evaluation for the UK indication. The ESC considered that the approach to extrapolation was unnecessarily complicated.
- 6.50 In the base case, PFS and OS data from FIRST were based on a subgroup of patients who were naïve to endocrine therapy in line with the UK indication, however the ITT population of FIRST is more applicable to the Australian setting which includes patients with prior endocrine therapy.
- 6.51 The submission also presented a sensitivity analysis that used a proportional hazards model, in which the hazard ratios from the meta-analyses of FIRST and FALCON (incorporating the efficacy of fulvestrant in the ITT population of FIRST) are applied to the extrapolated PFS and OS curves from the anastrozole arm in FALCON. The PBAC considered that use of the full ITT population from FIRST was more appropriate, consistent with the requested listing and noted that using this population (using a proportional hazards model) decreased the ICER slightly from \$55,000 to < \$75,000 to \$55,000 to < \$75,000/QALY based on a pooled HR for OS of 0.78 which includes the unadjusted results from FIRST. If the adjusted results from FIRST were included in the pooled analysis (OS HR of 0.82), the ICER increased to \$55,000 to < \$75,000/QALY.
- 6.52 The commentary and the ESC considered that use of the meta-analysis may not have been the best approach given the differences between FALCON and FIRST. The ESC considered that the FALCON trial should be the basis of the economic evaluation because it included only patients with HER2- disease. The ICER increases substantially when clinical data are taken only from FALCON. The pre-PBAC response stated that inclusion of the FIRST trial was reasonable as it included patients with prior endocrine therapies (in the proportional hazards sensitivity analysis) and reported mature OS data. The PBAC considered that both trials had limited applicability and it was reasonable to include the pooled data in the economic model (including patients in FIRST who received prior endocrine therapies).
- 6.53 Figure 6 compares the extrapolated PFS for fulvestrant and anastrozole based on the generalised gamma distribution with Kaplan-Meier data from the FALCON trial. While data from FIRST were also included in the base case of the model, the Kaplan-Meier data from FIRST is not included in the below figures (which were provided by the submission for model validation purposes). The model did not extrapolate PFS using the distribution with the best statistical fit (log-logistic), but selected the distribution based on visual inspection and clinical expert opinion. This is reasonable, and the ICER is not sensitive to the choice of distribution.

Figure 6: Observed PFS from FALCON versus modelled PFS for patients treated with fulvestrant and anastrozole for first-line treatment (model base case using non-proportional hazards model)

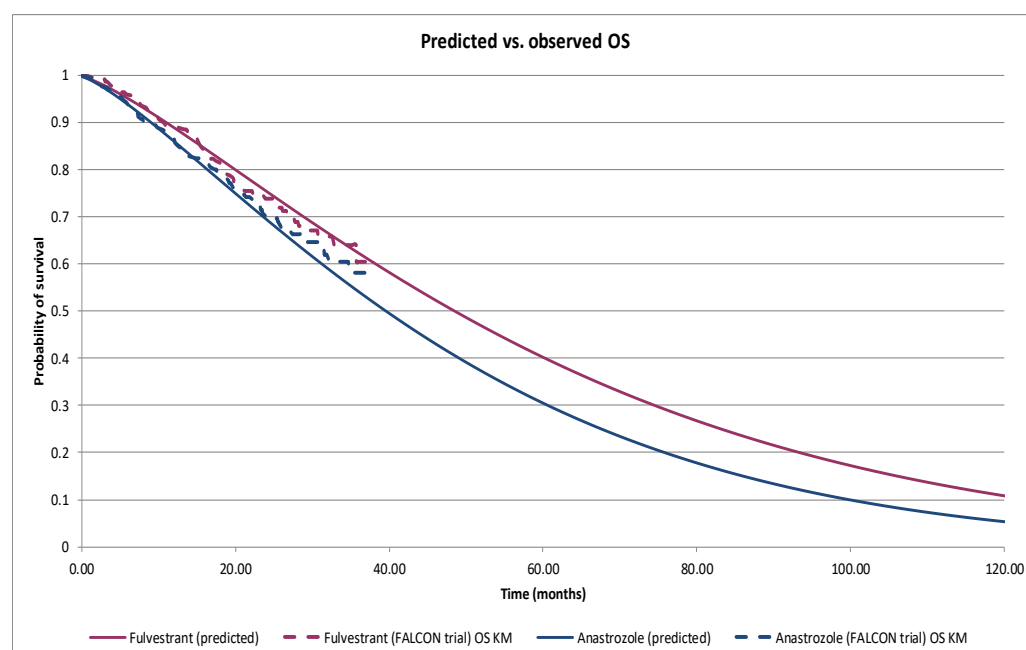


Source: Figure 3-8, p154 of the submission. Formatted during evaluation to a ten-year time horizon instead of 30-year time horizon using 'Results_validation' sheet in the submission Excel model.

KM = Kaplan Meier; PFS = progression free survival.

- 6.54 The model appears to overestimate PFS for fulvestrant slightly. The median difference in PFS in FALCON was 2.8 months, however the modelled predicted median difference in PFS was 4.6 months.
- 6.55 Figure 7 compares the extrapolated OS for fulvestrant and anastrozole based on the Weibull distribution with Kaplan-Meier data from the FALCON trial. While data from FIRST were also included in the base case of the model, the Kaplan-Meier data from FIRST is not included in the below figures (the figures were provided by the submission for model validation purposes).

Figure 7: Observed OS from FALCON versus modelled OS for patients treated with fulvestrant and anastrozole for first-line treatment (model base case using non-proportional hazards model)



Source: Figure 3-9, p155 of the submission. Formatted during evaluation to a ten-year time horizon instead of 30-year time horizon using 'Results_validation' sheet in the submission Excel model.
 KM = Kaplan Meier; PFS = progression free survival.

- 6.56 The modelled results appear to underestimate OS for the anastrozole arm. The predicted difference in median OS between the fulvestrant and anastrozole arms was about 8.3 months in the model, whereas in the FIRST ITT population it was 5.7 months. In addition, OS data from the FALCON trial are immature and therefore modelled OS is based mainly on OS data from FIRST which may not be applicable to the requested PBS population. The ESC considered that the approach to extrapolation appears to overestimate the incremental effectiveness of fulvestrant.
- 6.57 In the base case (non-proportional hazards model), time to treatment discontinuation (TTD) was based on PFS from FALCON. The PSCR noted that a sensitivity analysis using trial based time-on-treatment measured in FALCON resulted in a lower ICER than the base case (\$45,000 to < \$55,000 per QALY). This sensitivity analysis was based on the proportional hazards model (as TTD could only be applied in the proportional hazards model).
- 6.58 The ESC noted that, in the base case, the model used the extrapolated data for the full duration of the model. The ESC considered that the observed time to event data should have been used up to the time point at which the observed data became unreliable as a result of small numbers of patients remaining event-free, consistent with the PBAC Guidelines (paragraph 3A.4.3).
- 6.59 Table 14 presents the key drivers of the economic model.

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Table 14: Key drivers of the model

Description	Method/Value	Impact
Time horizon	10 years; extrapolated from 40 months. Reducing the time horizon to 7 years or 5 years increases the ICER.	High, favours fulvestrant.
Extrapolation model	In the base case, PFS and OS for fulvestrant and anastrozole treatment arms were estimated by a non-proportional hazards model and fitting parametric survival distributions to the PFS and OS trial data from the FALCON and FIRST trials, using a methodology that allowed a simultaneous extrapolation and meta-analysis of Kaplan-Meier curves from FALCON and FIRST trials. The ESC considered that the approach to extrapolation was unnecessarily complicated and noted that the ICER is highly sensitive to the choice of extrapolation approach (proportional hazards versus non-proportional hazards).	High, favours fulvestrant.
Trial data	Modelled gains in PFS and OS are based on the FALCON and FIRST trials. FIRST was open-label and lacked applicability to the proposed PBS population as it included patients with HER2+ (18%) and unknown HER2 status (34%).	High, favours fulvestrant.

Source: Compiled during evaluation.

DPMQ = dispensed price maximum quantity; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival.

6.60 The submission did not present a stepped analysis. The results of the economic evaluation are presented in Table 15.

Table 15: Results of the economic evaluation

	Fulvestrant	Anastrozole	Increment
Costs	\$ [REDACTED]	\$25,809	\$ [REDACTED]
Life years	4.08	3.53	0.56
QALYS	2.95	2.53	0.42
Incremental cost per life year gained			\$ [REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Source: Table 3-28, p156 of the submission. Added during evaluation from 'Results' sheet of the CEA excel model.

6.61 The submission stated that following a forecasted move to the F2 formulary the cost of fulvestrant will reduce by 25% reducing the ICER to \$35,000 to < 45,000 per QALY. The ESC considered that the entry of generic fulvestrant is not certain and has a substantial bearing on the cost-effectiveness of fulvestrant.

6.62 The results of key sensitivity analyses are summarised in Table 16.

6.63 The ICER is most sensitive to the model approach used to extrapolate PFS and OS data and the time horizon.

Table 16: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	0.42	\$ [REDACTED]
Time horizon (base case 10 years)			
• 5 years	\$ [REDACTED]	0.21	\$ [REDACTED]
• 7 years	\$ [REDACTED]	0.32	\$ [REDACTED]
PH model (using OS HR of 0.78, pooled data, unadjusted FIRST)	\$ [REDACTED]	0.40	\$ [REDACTED]
PH model (using OS HR of 0.82 pooled data, adjusted FIRST))	\$ [REDACTED]	0.32	\$ [REDACTED]
Non-PH model using best statistical fit and TTD (FALCON)	\$ [REDACTED]	0.03	\$ [REDACTED]
Non-PH model using best statistical fit (FALCON)	\$ [REDACTED]	0.03	\$ [REDACTED]
PH model using best statistical fit and TTD (FALCON)	\$ [REDACTED]	0.18	\$ [REDACTED]
PH model using best statistical fit (FALCON)	\$ [REDACTED]	0.18	\$ [REDACTED]
Multivariate sensitivity analysis			
PH model (using OS HR of 0.82); PLUS TTD based on trial	\$ [REDACTED]	0.32	\$ [REDACTED]
PH model (using OS HR of 0.82); PLUS Time horizon of 7 years, PLUS TTD based on trial	\$ [REDACTED]	0.24	\$ [REDACTED]

Source: Table 3-25, pp214-216 of the submission. Conducted during the evaluation.

ICER = incremental cost-effectiveness ratio; MMRM = mixed models with repeated measurements; OS = overall survival; PFS = progression free survival; PH = proportional hazards; QALY = quality-adjusted life-year; TTD = time to treatment discontinuation.

The redacted table shows ICERs in the range of \$55,000 to < \$75,000 per QALY, to \$555,000 to \$655,000 per QALY.

6.64 The ESC considered that the base case ICER appeared to have been underestimated for the following reasons:

- The FALCON trial is more applicable to the requested population. The ICER was greater than \$100,000 per QALY for all reasonable scenario analyses that used clinical data only from FALCON.
- The median follow-up in FALCON was 13.8 months (in the fulvestrant arm), at which point 69% of patients were still alive. The extrapolation of relatively immature trial data to 10 years increased the inherent uncertainty in the model. The ESC considered that the 10 year time horizon may be too long, given the lack of high quality, long term data available and given that the HR for OS hazard ratio in FALCON was not statistically significant (HR: 0.875 (95% CI: 0.629, 1.217)).
- The ICER was highly sensitive to the approaches used to estimate PFS and OS. The base-case model used the non-proportional hazards model and data from the meta-analysis of FALCON and FIRST and did not use the best statistical fit for extrapolating PFS.
 - Selecting the non-proportional hazards model and using FALCON data, the best statistical fit and TTD, the ICER increased from \$55,000 to < \$75,000 per QALY to \$555,000 to < \$655,000 per QALY.

- Selecting the proportional hazards model and using FALCON data, the best statistical fit and TTD the ICER increased from \$55,000 to < \$75,000 per QALY to \$95,000 to < \$115,000 per QALY. The ESC considered the proportional hazards model, using FALCON and the best statistical fit (with or without TTD) was the most reasonable approach.

Economic analysis (second-line)

- 6.65 The submission presented a cost-minimisation analysis comparing fulvestrant to EVE+EXE as second-line treatment for HR+ HER2- advanced breast cancer.
- 6.66 The ESC considered the clinical claim of non-inferiority was not supported by the evidence and therefore, a cost-minimisation analysis was unlikely to be appropriate.
- 6.67 The ESC also considered that other treatment options are available in the second/subsequent-line setting (e.g. tamoxifen and capecitabine), and therefore a cost-minimisation analysis versus EVE+EXE may not be appropriate.
- 6.68 The proposed equi-effective doses were based on the dose frequency and median duration of treatment in the pivotal clinical trials (CONFIRM and BOLERO-2). The submission estimated the equi-effective doses as:
- fulvestrant 500 mg per month over 5.70 months plus an additional loading dose of fulvestrant in the first month, is equivalent to
 - everolimus 8.6 mg daily over 5.50 months plus exemestane 25 mg daily over 6.78 months.
- 6.69 The submission included the cost of administration and costs of adverse events. Table 17 presents the results of the cost-minimisation analysis.

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Table 17: Results of the cost-minimisation analysis

Component	Fulvestrant	EVE + EXE	
		EVE	EXE
Medicine costs			
PBS item	N/A	2985D 2819J	10103R
DPMQ ^b	\$█ ^a	\$1,727 (10 mg) \$892 (5 mg)	\$67
Duration of treatment*	5.7 months	5.50 months	6.78 months
Packs per course of treatment	6.70	5.58	6.88
Total cost per course of treatment	\$█	\$8,325.68	\$461.05
		\$8,787	
Additional costs			
Administration ^c	\$65.33	\$0.00	
Adverse events ^d	\$0.00	\$1,477	
Total cost per patient	\$█ ^a	\$10,264	
Cost saving per patient to PBS		\$█	
Overall cost saving per patient (including administration and adverse events)		\$█	

Source: Table 3-35 to 3-36, p164-165 of the submission.

EVE = everolimus; EXE = exemestane

*Duration of treatment was based on median duration of exposure. CONFIRM trial is still ongoing and expected to end in December 2020.

^a The submission stated that the price of fulvestrant would reduce to AEMP \$584.96 following a move to the F2 formulary. In this case, the overall cost of fulvestrant would be \$4,461.53, which equates to a cost saving per patient of \$4,390.52 to the PBS and \$5,802.06 overall if fulvestrant were to be used in place of everolimus plus exemestane.

^b The cost-minimisation analysis was conducted at the DPMQ level. However, cost-minimisation analyses should be conducted at the AEMP level.

^c Based on expert clinical advice, fulvestrant would be administered by a nurse. The cost of a nurse practitioner visit (MBS item 82200: \$9.75) is included in the analysis as an administration cost for fulvestrant (twice in the first cycle and then once per subsequent cycles). This was multiplied by the packs per course of treatment for fulvestrant (6.70).

^d Grade 3/4 adverse events occurring in ≥5% patients. Adverse events included stomatitis, fatigue, dyspnoea, anaemia, hyperglycaemia and gamma-glutamyl transferase. Unit costs based on Australian Refined Diagnosis Related Groups (AR-DRGs) for all adverse events except anaemia. Anaemia unit costs based on MBS and PBS items.

6.70 For second-line treatment, the overall cost of fulvestrant per patient was estimated to be \$█ based on the proposed effective DPMQ (see Table 17). The submission stated that following a forecasted move to the F2 formulary, which would trigger a 25% reduction to the fulvestrant price, the overall cost of fulvestrant per patient would be \$█.

6.71 The treatment durations of fulvestrant and EVE+EXE were compared naively. Instead, the commentary considered that an adjusted indirect comparison of treatment durations should have been performed, using the evidence network connecting the two treatments. The PSCR argued that the approach used in the submission was conservative and presented the results of an adjusted comparison of treatment durations, which resulted in an increased duration of treatment with EVE+EXE, which would increase the cost savings in the cost-minimisation analysis (from a cost saving per patient to the PBS of \$█ to \$█).

6.72 The commentary and ESC considered that the calculated cost-savings per patient shown in Table 17 should be considered with caution due to the following:

- Only median treatment durations were considered; it would have been more

appropriate to model full time on treatment distributions.

- The cost-minimisation analysis assumed different treatment durations for EVE+EXE. Wastage for EVE+EXE was also not considered.
- The adverse events costs for fulvestrant are uncertain given CONFIRM did not report results for some AEs reported by BOLERO-2 trial.
- The ESC considered that the nurse administration item (MBS item 82200: \$9.75) is not appropriate and underestimates the administration costs for fulvestrant.

Drug cost/patient/course

6.73 The drug cost per patient per course for fulvestrant monotherapy in the second-line setting was estimated to be \$ [REDACTED] (see Table 17).

Estimated PBS usage & financial implications

6.74 This submission was considered by DUSC. The submission used an epidemiological approach. The submission presented an aggregated budget impact for both first-line and second-line treatment, and did not present results separately for each line. Table 18 outlines the key inputs in the financial estimates.

Table 18: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Estimated incidence of breast cancer in women Australia, 2019	19,371	AIHW Cancer in Australia 2019 Chapter 5 Incidence. Table S5.3	The commentary considered that this was reasonable.
Estimated incident growth rate	3.52%	AIHW 2019 ACIM data book	The commentary considered that this was reasonable.
Proportion of incident cases in females ≥40 years	95%	AIHW Cancer in Australia 2019, Table S5.3	DUSC considered it was not reasonable to exclude patients aged ≤40 years who may be induced into menopause.
Proportion of breast cancers in women 40 years and above with ABC (stage 3 (advanced) or stage 4 (metastatic)) in Australia	17%	AIHW Cancer in Australia 2019, Table S3.1	The PBAC noted that this was not consistent with DUSC and ESC advice that only patients with unresectable (inoperable) stage 3 and stage 4 patients should be included in the listing.
Proportion of all breast cancers that are HR+ and human epidermal growth factor receptor 2 negative (HER2-)	70%	Boyle et al. 2018	
Proportion of patients receiving first-line treatment	100%	Assumption	The commentary considered that this was reasonable.

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Data	Value	Source	Comment
First-line treatment			
Proportion of first-line patients treated with:			
CDK4/6 inhibitors + NSAI	80.39%	PBS data for palbociclib (May 2019 to Dec 2019) to project CDK4/6 inhibitor utilisation as a proportion of eligible patients in 2020 Assumption from Twelves 2020 Calculated as remaining patients not treated with either CDK4/6 inhibitor +NSAI or chemotherapy	Palbociclib was listed in May 2019 so the data were still immature. The commentary considered that data for ribociclib should have been used. It is uncertain whether these estimates from a UK cohort study apply to the Australian setting. DUSC considered the proportion of patients treated with first line endocrine monotherapy (4%) was underestimated; DUSC estimated it to be 10 to 15%. However DUSC considered this underestimate was more than cancelled out by the overestimate of the fulvestrant uptake rate.
Chemotherapy (patients with visceral metastases)	16%		
Endocrine monotherapy	4%		
Fulvestrant uptake rate (from endocrine monotherapy population only)	Yr 1 50% Yr 2 60% Yr 3+ 70%	Unclear	DUSC considered that patients treated with single agent NSAI in the first line setting, who are considered to be too frail to tolerate the additional toxicity of CDK4/6 inhibitors, are less likely to elect to have a parenteral therapy as their initial treatment. Thus, the fulvestrant uptake of 70% by year 3 is significantly overestimated.
Fulvestrant first-line scripts per course of treatment	22.89	Calculated from Section 3A based on FALCON – extrapolated time to treatment discontinuation	The submission assumed that every initiating patient receives 22.89 scripts per year, however the commentary considered that the number of scripts per patient should have been distributed over the actual years in which scripts would be required.
NSAI first-line scripts per course of treatment	17.98	Calculated from Section 3A based on FALCON - extrapolated time to treatment discontinuation	DUSC considered the duration of treatment was overestimated as FALCON included patients who had no prior endocrine therapy who are more likely to have a prolonged response than those with prior treatment for early breast cancer. DUSC further noted that the treatment duration was calculated from time to discontinuation rather than the mean number of treatments.
Second-line treatment			
Proportion of patients receiving second-line treatment	89%	AIHW 2018, Cancer data Table 7b	The commentary considered that this was reasonable.
Proportion of second-line patients treated with:			Since the DUSC 2017 report other medications such as CDK4/6 inhibitors have entered the market. Given the adverse events associated with EVE+EXE and entry of CDK4/6 inhibitors, the number of patients on EVE+EXE may be overestimated. DUSC considered use of EVE has declined over time and the estimates of current EVE use are overestimated.
EVE+EXE	46%	Everolimus DUSC 2017; Kursoky 2018, p. e533 Figure 1	
Chemotherapy	37%	Kurosky 2018, p.e533 Figure 1	

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Data	Value	Source	Comment
Endocrine monotherapy	17%	Assumption	The submission assumed the remaining proportion (17%) would be treated with endocrine monotherapy without any justification.
Uptake rates (displacement of EVE+EXE)	Yr 1 50% Yr 4+ 80%	Unclear	DUSC considered that the assumption that fulvestrant would displace 80% of EVE+EXE use by year 4 is significantly overestimated and not justified in the submission
Fulvestrant second-line scripts per course of treatment	6.7	Section 3B. CONFIRM median duration of treatment + loading dose	The commentary considered that this was reasonable.
EVE+EXE scripts per course of treatment: Everolimus	5.58	Section 3B. BOLERO-2 (Yardley 2013)	This is inconsistent with Section 3A where patients receive targeted second-line treatment of EVE+EXE for 23.90 weeks (5.58 months). It is not clear why the submission split the treatment duration on EVE and EXE in Section 3B and Section 4.
Exemestane	6.88		
Chemotherapy second-line scripts per course of treatment (assumed capecitabine)	6.73	Kurosky 2018	
NSAI second-line scripts per course of treatment	5.78	Assumed same median duration of treatment as fulvestrant second-line (CONFIRM)	The commentary considered that this was reasonable.

Source: Tables 4.1, & 4.10, pp166-167 & 175 of the submission; Fulvestrant financial estimates workbook, 'Registry population' worksheet. ABC = advanced breast cancer; ACIM = Australia Cancer Incidence and Mortality; AEMP = average ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; CDK4/6 = cyclin dependant kinase 4/6; DPMQ = dispensed price maximum quantity; DUSC = Drug Utilisation Sub Committee; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; IV = intravenous; NSAI = non-steroidal aromatase inhibitor; PBS = pharmaceutical benefits scheme; PO = oral administration.

6.75 The estimated use and financial implications for a first-line and second-line listing of fulvestrant are presented in Table 19.

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Table 19: Estimated use and financial implications first- and second-line treatment combined

	Year 1 2021	Year 2 2022	Year 3 2023	Year 4 2024	Year 5 2025	Year 6 2026	Total
Total fulvestrant patients for first-line and second-line	█	█	█	█	█	█	█
Total fulvestrant prescriptions for first-line and second-line (PBS/RPBS)	█	█	█	█	█	█	█
Estimated total cost of fulvestrant to the PBS/RPBS (using effective DPMQ of \$█)							
Cost of fulvestrant to PBS	\$█	\$█	\$█	\$█	\$█	\$█	\$█
Cost of changed PBS medicines	-\$█	-\$█	-\$█	-\$█	-\$█	\$█	-\$█
Net cost to PBS	\$█	\$█	\$█	\$█	\$█	\$█	\$█
Cost of fulvestrant to the RPBS	\$█	\$█	\$█	\$█	\$█	\$█	\$█
Cost of changed medicines	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Net cost to RPBS	\$█	\$█	\$█	\$█	\$█	\$█	\$█
Net cost PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to Government (effective)	\$█	\$█	\$█	\$█	\$█	\$█	\$█

Source: Table ES 10 of executive summary which is inclusive of the MBS costs for administering injections
 PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme.

The redacted table shows that at Year 6, the estimated number of patients was 5,000 to < 10,000, and the estimated number of prescriptions was 40,000 < 50,000.

- 6.76 The total cost to the PBS/RPBS of fulvestrant, at the effective DPMQ proposed in the submission, was estimated to be \$40 million to < \$50 million in the first 6 years of listing. Including offsets, the net cost to the PBS/RPBS/MBS was estimated to be \$0 to < \$10 million over 6 years.
- 6.77 The commentary noted that script numbers for fulvestrant assumed that every initiating patient receives 22.89 scripts per year, which may not be reasonable.
- 6.78 The PBAC considered that the estimated cost-offsets were not likely to be realised because for most patients fulvestrant would add an additional line of therapy.
- 6.79 The submission included < 500 grandfathered patients who would transition from the Access Program to PBS supply of fulvestrant and assumed all patients would require the same number of scripts as incident patients using second-line treatment (p173 of the submission). The submission did not provide any information on the Patient Access Program so the number of patients using first-line or second-line fulvestrant therapy is not clear, and the number of scripts required for first-line and second-line treatment for grandfathered patients is uncertain. The PBAC also considered that it was unclear how many of these grandfathered patients may have been receiving fulvestrant in combination with ribociclib or other CDK4/6 inhibitors.

- 6.80 DUSC considered that overall there was a net overestimate of fulvestrant utilisation. However if the restriction is changed to include “The condition must be inoperable”, as suggested by DUSC and ESC, the first line overestimate becomes smaller and the second and subsequent line use of fulvestrant will mean there is a net underestimate. A disaggregated budget impact for the first-line and second-line treatment of fulvestrant would be required to assess the impact of listing fulvestrant monotherapy for the two different settings.
- 6.81 In the first line setting, DUSC considered that the uptake of fulvestrant was overestimated driven primarily by the large resectable stage III population who would be eligible under the proposed restriction but this population was excluded from the key FALCON trial. DUSC further considered that patients unable to tolerate CDK4/6 inhibitor treatment were less likely to elect a parenteral therapy as their initial treatment. Thus, DUSC considered that uptake of 70% by Year 3 was significantly overestimated.
- 6.82 DUSC considered the duration of treatment (17.98 scripts per course) was overestimated. DUSC noted that the FALCON trial included only hormonal therapy naïve patients who are more likely to have a prolonged response than those with prior treatment for early breast cancer. DUSC further noted that the treatment duration was calculated from time to discontinuation rather than the mean number of treatments.
- 6.83 In the second (and subsequent) line setting, DUSC considered the financial impact was underestimated as the estimates assumed that patients receiving chemotherapy and endocrine therapy will not then subsequently receive fulvestrant. DUSC considered that fulvestrant may add an additional line of treatment rather than substituting existing listings. Further, DUSC noted that the utilisation of everolimus had declined over time, and as such, the submission had overestimated cost offsets from substitution of everolimus.

Quality Use of Medicines

- 6.84 DUSC considered that, whilst toxicities observed in clinical trials were similar between aromatase inhibitors and fulvestrant, additional adverse events including injection site pain and liver function test abnormalities can result from fulvestrant. The submission did not detail a recommended liver function monitoring schedule.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of fulvestrant for the treatment of patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) unresectable advanced or metastatic breast cancer (ABC). The PBAC was satisfied that first line treatment with fulvestrant provides, for some patients, an improvement in efficacy over NSAI. The PBAC also considered, on balance, fulvestrant

provides acceptable effectiveness and potentially increased safety and tolerability versus EVE+EXE in subsequent lines of therapy. The PBAC considered that the magnitude of benefit for first line treatment with fulvestrant was uncertain due to limitations in the trial data and its applicability to the PBS population. This resulted in uncertainty in the ICER presented, which the PBAC considered could be addressed through a price reduction to achieve an ICER in the range of \$45,000/QALY to \$50,000/QALY. The PBAC considered that a corresponding reduction in price for subsequent line use was also appropriate, given the high level of uncertainty in the clinical evidence presented.

- 7.2 The PBAC recalled that it, along with the BCNA and MOGA Breast Cancer Expert Group, had requested that the sponsor provide a submission for fulvestrant. The PBAC considered that the main clinical need for fulvestrant monotherapy was:
- In the first-line setting: older or frail patients who wish to avoid CDK4/6 inhibitors or who are intolerant to CDK4/6 inhibitors, or patients who progressed on NSAIs in the adjuvant setting, and
 - In the second-line and subsequent-line setting: patients who received CDK4/6 inhibitors in combination with NSAIs in first-line.

The PBAC considered that there would be relatively few patients in each of these groups.

- 7.3 The PBAC considered that, although there is a clinical place for fulvestrant monotherapy, the clinical need for its use in combination with CDK4/6 inhibitors is higher as combination therapy is preferred for patients who are able to tolerate it. This was consistent with comments received from the BCNA and MOGA Breast Cancer Expert Group regarding the clinical need for fulvestrant.
- 7.4 While the evidence presented was for use of fulvestrant as monotherapy, the proposed listing would not specifically prohibit use in combination with other medicines, such as CDK4/6 inhibitors and this use would be consistent with the TGA indications for some CDK4/6 inhibitors. However, such use is prohibited in the current CDK4/6 inhibitor restrictions, which state ‘treatment must be in combination with anastrozole or letrozole’. The PBAC reiterated the main clinical need for fulvestrant was in combination with CDK4/6 inhibitors but noted that the clinical evidence, cost-effectiveness and financial impacts of combination use were not presented in this submission. The combination of ribociclib plus fulvestrant was considered as part of ‘Agenda Item 6.06 ribociclib’ at the same meeting.
- 7.5 The PBAC considered that the proposed line-agnostic listing for fulvestrant was appropriate, given the clinical need across the settings. While broader than the current and requested TGA indications, the PBAC considered that a line-agnostic listing was appropriate in this particular case given clinician familiarity with fulvestrant in these settings, and would be consistent with National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines, and consistent with the PBS listing for exemestane. The PBAC further noted that the

requested TGA indication would not cover all the off-label settings in which listing was requested (i.e. it would not include use in progressive disease following therapies other than tamoxifen).

- 7.6 The PBAC agreed with the ESC and DUSC that the listing should require the condition to be unresectable, consistent with the patient population included in the clinical evidence presented.
- 7.7 The submission estimated that < 500 patients on a Patient Access Program would be eligible to receive PBS-funded treatment and requested a grandfather listing for these patients. However, it was not clear whether this estimate included patients treated with fulvestrant in combination with CDK4/6 inhibitors (who would not be eligible for PBS-subsidised fulvestrant). The PBAC noted that there are no criteria in the recommended restrictions that would prevent patients treated with fulvestrant monotherapy under the patient access program from accessing PBS-subsidised treatment, therefore a separate grandfather listing is not required.
- 7.8 The PBAC considered that in the first line setting anastrozole was the appropriate comparator. The PBAC considered that in subsequent lines of treatment EVE+EXE was the most appropriate comparator, while acknowledging that there are other treatments used in this setting, such as tamoxifen and chemotherapy.
- 7.9 The clinical evidence in the first line setting was based on two trials: FALCON and FIRST. While the FIRST trial demonstrated a statistically significant improvement in OS (unadjusted results), it was open-label and the PBAC considered that it lacked applicability to the proposed PBS population as it included patients with HER2+ (18.5%) and unknown HER2 status (34%). While the pre-PBAC response claimed that HER2 is not a treatment effect modifier (based on trials that did not include fulvestrant), the PBAC considered that this increased uncertainty in the applicability of the outcomes. The PBAC noted that the FALCON trial was larger and more recent and only included HER2- patients, consistent with the proposed listing. However, the OS data were immature (with 69% of patients still alive at the data cut) and the OS hazard ratio was not statistically significant, 0.875 (95% CI: 0.629, 1.217). However, FALCON excluded patients who had prior endocrine therapy and therefore was only applicable to patients with de novo advanced or metastatic disease; whereas in the Australian setting only around one-third of patients with metastatic breast cancer present with de novo metastatic disease. As such, the PBAC considered that both trials had limited applicability to the requested PBS population and noted that the pooled OS hazard ratio from the meta-analysis of FALCON and FIRST (with the FIRST results adjusted for baseline characteristics in a Cox proportional hazards model) resulted in a HR of 0.82 (95% CI: 0.65, 1.04).
- 7.10 The PBAC noted that patients with visceral disease are less likely to be treated with fulvestrant (or any endocrine treatment) and more likely to be treated with chemotherapy, but these patients were included in both FALCON and FIRST trials. The PBAC noted that subgroup results presented in the PSCR suggested that fulvestrant

had a greater relative treatment effect in patients with non-visceral disease compared with visceral disease.

- 7.11 The PBAC considered that the claim of superior comparative effectiveness compared with anastrozole in first line treatment was reasonable, however a robust conclusion regarding the magnitude of benefit for fulvestrant compared with anastrozole was complicated by the limited applicability of both the trials, the risk of bias in the FIRST trial (due to the open-label design) and the immaturity of the FALCON trial. The PBAC considered that the claim of non-inferior safety compared with anastrozole may be reasonable, based on the limited data available.
- 7.12 The PBAC noted that the comparison of fulvestrant with EVE+EXE in second and subsequent line treatment was based on an informal indirect comparison, using five separate studies. The PBAC noted that a formal comparison was not presented as the primary evidence due to significant heterogeneity between the studies in the second-line setting, particularly in terms of HER2 status and the number of prior therapies, and there was variability in PFS and OS results in the control arms of the trials. The PBAC also considered the applicability was limited given that many of the trials included patients who were not HER2-. The PBAC also noted that the results of the BOLERO-2 trial (EXE vs EVE+EXE) were difficult to interpret as there was no statistically significant improvement in OS and many patients discontinued from combination therapy due to toxicity. Overall, the PBAC considered that the informal indirect comparison did not allow a meaningful comparison of outcomes with fulvestrant versus EVE+EXE.
- 7.13 The PBAC noted that an adjusted indirect comparison was also presented which suggested that fulvestrant may be inferior to EVE+EXE in terms of PFS whereas there was a trend to superior OS for fulvestrant. Overall, the PBAC considered that the adjusted indirect comparison was difficult to interpret as the transitivity assumption was likely to have been violated.
- 7.14 The PBAC considered that fulvestrant appears to have superior safety compared with EVE+EXE, noting the interpretation of the safety data was difficult due to the limitations of the clinical trial data and the incomplete reporting of adverse events in the trials. The PBAC considered that the claim of non-inferior comparative effectiveness compared with EVE+EXE was not well-supported by the data given the differences between the trials. However, overall, the PBAC considered that, in light of the superior comparative safety and likely similar efficacy to EVE+EXE, there was likely a clinical benefit to fulvestrant in particular groups of patients. The PBAC came to this conclusion in the context of the lower price than EVE+EXE and the likely limited use in this setting.
- 7.15 In the economic model in the first-line setting, the PBAC noted that the ICER was high (above \$100,000/QALY) when only data from FALCON were applied, but considered it was reasonable to include the pooled data in the economic model given that both trials had limited applicability to the requested PBS population. The PBAC noted that

the base case of the economic model excluded the clinical data for the 25% of patients in FIRST who had received prior therapy for early disease, and considered this was not reasonable as these patients would be eligible for PBS-subsidised fulvestrant. As such, the PBAC considered it would be more reasonable to use the ITT results from FIRST, which would require use of the proportional hazards model that was provided as a sensitivity analysis in the submission.

- 7.16 The base case ICER presented in the submission was \$55,000 to < \$75,000/QALY, however the PBAC considered that there was substantial uncertainty in this ICER due to limitations with the clinical data as outlined above. Given this uncertainty, the PBAC considered an ICER in the range of \$45,000/QALY to \$50,000/QALY would be acceptably cost-effective. Further, the PBAC considered that a time horizon of 7 years would be more appropriate given the extrapolation of relatively immature trial data from FALCON to 10 years increased the inherent uncertainty in the model. Further, a time horizon of 7 years would be consistent with the Committee's consideration of other treatments in a similar patient population.
- 7.17 The PBAC considered that the most appropriate base case for the economic model would use: pooled data from FALCON and FIRST (ITT of FIRST adjusted for baseline characteristics) which resulted in an OS HR of 0.82 (which required use of the proportional hazards approach); treatment duration based on the trial time to treatment discontinuation; and a 7 year time horizon. The PBAC noted that a reduction in the price of fulvestrant would be required to achieve an acceptable ICER of \$45,000/QALY to \$50,000/QALY.
- 7.18 In the cost-minimisation analysis presented for the second-line setting, the PBAC noted that the cost for fulvestrant was lower than EVE+EXE. The PBAC considered it was appropriate that the cost for fulvestrant should be substantially lower than EVE+EXE, given the uncertain claim of non-inferior effectiveness but in the context of a potential safety advantage, and in this context, the PBAC considered that it would be appropriate to list fulvestrant at the same price as considered cost-effective in the first-line setting (refer to Paragraph 7.17). The PBAC noted that DUSC considered that fulvestrant would not necessarily replace EVE+EXE, which is likely to be used in later lines of therapy and as such the cost-savings estimated in the cost-minimisation are unlikely to be realised.
- 7.19 The PBAC considered that the submission had overestimated the likely utilisation of fulvestrant, in particular the PBAC agreed with DUSC that:
- utilisation of fulvestrant in the first line was overestimated driven primarily by the large resectable stage III population who the PBAC considered should be excluded;
 - patients unable to tolerate CDK4/6 inhibitor treatment were less likely to elect a parenteral therapy as their initial treatment;
 - the duration of treatment (17.98 scripts per course) was overestimated as it was based on the FALCON trial which included only hormonal therapy naïve patients

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who are more likely to have a prolonged response than those with prior treatment for early breast cancer.

- 7.20 The PBAC agreed with DUSC that in the second (and subsequent) line setting the financial impact was underestimated as the submission had assumed that patients receiving chemotherapy and endocrine therapy will not then subsequently receive fulvestrant. The PBAC considered that where fulvestrant adds a line of therapy, cost-offsets will be less than was estimated in the submission. Further, DUSC noted that the utilisation of everolimus had declined over time, and as such, the submission had overestimated cost offsets from substitution of everolimus.
- 7.21 On balance, the PBAC considered that the submission had overestimated the utilisation of listing fulvestrant as the impacts outlined in Paragraph 7.19 would outweigh those outlined in Paragraph 7.20. The PBAC considered that the estimated cost-offsets were not likely to be realised because for most patients fulvestrant would be an additional line of therapy. Overall, the PBAC considered that the net financial impact is likely to be relatively small. The PBAC also noted that financial estimates for fulvestrant would be impacted if combination therapy with CDK4/6 inhibitors becomes available on the PBS.
- 7.22 The PBAC recommended that fulvestrant should not be treated as interchangeable with any other drugs.
- 7.23 The PBAC advised that fulvestrant is not suitable for prescribing by nurse practitioners.
- 7.24 The PBAC recommended that the Early Supply Rule should not apply.
- 7.25 The PBAC found that the criteria prescribed by the National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for fulvestrant:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over NSAIs. The PBAC considered this criteria was not met as the available data did not allow a reliable assessment of the magnitude of the incremental benefit;
 - b) The treatment is not expected to address a high and urgent unmet clinical need; and
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.26 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new medicinal product:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FULVESTRANT fulvestrant 250 mg/5 mL pre-filled syringe, 2	NEW	1	1	5	Faslodex
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new code)					
Indication: Locally advanced or metastatic breast cancer					
Clinical criteria: The condition must be hormone receptor positive AND The condition must be human epidermal growth factor receptor 2 (HER2) negative AND The condition must be unresectable AND					
Population criteria: Patient must not be pre-menopausal.					
Prescribing Instructions: A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. Special pricing arrangements apply					

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.