

**7.08 ULIPRISTAL ACETATE,  
Tablet, 5 mg,  
Esmya®, Vifor Australia Pty Ltd.**

**1 Purpose of Application**

1.1 The resubmission requested a Section 85, Authority Required (Streamlined) listing for ulipristal for the treatment of moderate to severe symptoms of uterine fibroids prior to planned surgery. This is the second submission to the PBAC.

**2 Requested listing**

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough. The Pre-Sub-Committee Response (PSCR) included changes to the requested listing which are added in bold.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ULIPRISTAL ACETATE Tablet 5 mg, 28	1	2	\$ [REDACTED]	Esmya® Vifor Australia Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Acute
<b>Severity:</b>	Moderate to severe
<b>Condition:</b>	<i>Symptomatic</i> uterine fibroids
<b>PBS Indication:</b>	<del>Acute management of moderate to severe symptomatic of uterine fibroids prior to planned surgery</del>
<b>Treatment phase:</b>	<del>Initial treatment</del>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> <i>Authority Required - Telephone</i> <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> <i>Streamlined</i>
<b>Treatment criteria:</b>	Must be treated by, or <del>under the direction of,</del> <i>in consultation with,</i> a gynaecologist.

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<b>Clinical criteria:</b>	<p>Patients must be eligible for <i>surgery</i>;  AND  Patients must be planning surgery;  AND  Patient must have other factors which would make surgery technically difficult,  OR  Patient must have other factors which would unnecessarily delay immediate surgery;  AND  Patient must have <b>at least 1 fibroid <math>\geq 3</math> cm in diameter confirmed by ultrasound and/or multiple fibroids,</b>  AND/OR  Patient must have <b>at least 3 fibroids confirmed by ultrasound <del>multiple fibroids</del>;</b>  AND  Patient must have <del>significant bleeding</del> <b>heavy menstrual bleeding that negatively affects quality of life,</b>  OR  Patient must have <del>significant anaemia</del> <b>confirmed anaemia defined as haemoglobin <math>\leq 120</math> g/L,</b>  AND  Treatment must not be more than 3 months.</p>
<b>Population criteria:</b>	Patient must be eligible for and planning surgery for uterine fibroids
<b>Prescriber Instructions</b>	<p><del>No more than one three-month cycle of therapy will be authorised within 18 months</del>  Only one PBS-subsidised treatment cycle is allowed every 18 months should this condition recur.</p> <p>No increase in the maximum quantity or number of repeats may be authorised.</p>

- 2.2 The proposed listing was consistent, although narrower (in terms of patient characteristics and limits on the number of treatment cycles within certain timeframes), than the approved TGA indication of “intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age”. The TGA approved Product Information (PI) for ulipristal recommends treatment courses of up to 3 months each and re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion. It is noted in the PI that repeated intermittent treatment has been studied up to 4 intermittent treatment courses.
- 2.3 The requested restriction in the previous submission did not require patients to be eligible for and planning surgery for uterine fibroids, although the sponsor proposed to narrow the requested restriction to this patient population in their Pre-PBAC response for the July 2016 submission.
- 2.4 The ESC considered clarification is required to define the criteria regarding what constitutes a ‘technically difficult’ surgery. The PBAC discussed that exclusion criteria may be easier to define, for example including a criterion that patients cannot use or have failed other methods to reduce uterine fibroid size and menstrual bleeding would help narrow the population.
- 2.5 The ESC considered that it may not be reasonable to limit the use of ulipristal to one course of 3 months of treatment every 18 months. It was noted this would particularly be an issue for those women who would be unable to proceed to surgery within the 3 month timeframe. It was thought that this may lead to equity issues for women

treated in public and private settings given that waiting time to surgery in public hospitals may exceed 3 months. However, no data are available regarding the comparative effectiveness or safety of ulipristal versus placebo for continued use beyond 3 months. The pre-PBAC response contended that the single 3 month course proposed in the restriction is consistent with the available clinical data, and will generally provide four to six months relief from moderate to severe symptoms of fibroids, which represents a sufficient bridge given the average waiting times across the Australian public hospital system. It was noted that longer waiting times could potentially be managed by allowing an increase in the number of repeats authorised. The sponsor considered the proposed restriction discourages de facto use as a long-term intermittent regimen while not excluding treatment of the significant proportion of patients who experience a recurrence of their fibroids following surgery or surgical substitute interventions.

- 2.6 In the PSCR the sponsor acknowledged and agreed that an Authority Required (telephone) restriction may be required given the issues identified by the Secretariat regarding tracking patients treated within the previous 18 months.
- 2.7 A specific requirement for diagnosis by ultrasound or magnetic resonance imaging (MRI) is not included in the restriction. There are also no criteria defining moderate to severe symptoms. The PSCR stated that the restriction could include ultrasound to confirm diagnosis of uterine fibroids, noting that MRI is typically recommended only as a second line investigation for large or indeterminate masses, or where malignancy is a possibility.
- 2.8 The resubmission was based on a cost-utility analysis of ulipristal compared with placebo.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### 3 Background

- 3.1 **TGA status at time of PBAC consideration:** ulipristal was TGA registered on 17 May 2016 for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- 3.2 Ulipristal was previously considered by the PBAC for the treatment of moderate to severe symptoms of uterine fibroids in July 2016.
- 3.3 A summary of the differences between the July 2016 submission and the resubmission is provided in the table below.

**Table 1: Summary of the July 2016 submission and the resubmission**

	July 2016 submission	Resubmission
Requested restriction	Moderate to severe symptoms of uterine fibroids. The requested listing was based on the clinical setting of both short and long-term management, however the sponsor requested in the Pre-PBAC response to narrow the listing to short-term therapy prior to planned surgery (paragraph 2.1). <b>PBAC comment:</b> All of the originally requested	Moderate to severe symptoms of uterine fibroids prior to planned surgery. Prescriber instructions: “No more than one three-month cycle of therapy will be authorised within 18 months”.

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	July 2016 submission	Resubmission
	treatment scenarios were considered, however the PBAC took note of the sponsor's Pre-PBAC request.	
DPMQ	\$██████	\$██████ Reduced to \$██████ in prePBAC response.
Main comparator	Goserelin <b>PBAC comment:</b> As an adjunct to surgery, goserelin may be an appropriate comparator, however it is not listed on the PBS for use in uterine fibroids and the cost-effectiveness for this indication has not been assessed. No treatment (or placebo) is the appropriate main comparator. The comparison should include the impact of treatment on surgical outcomes (paragraph 7.4).	Placebo (no treatment, prior to planned surgery).
Clinical evidence	For the short-term surgery population, the clinical evidence provided was: <ul style="list-style-type: none"> <li>PEARL I: double-blind, RCT comparing ulipristal 5 mg (n=96) and ulipristal 10 mg (n=98) to placebo (n=48) for 3 months in women who were eligible to undergo surgery for uterine fibroids.</li> <li>PEARL II: double-blind, non-inferiority RCT comparing ulipristal 5 mg (n=102) and ulipristal 10 mg (n=103) to leuprorelin (n=102) for 3 months in women who were eligible to undergo surgery for uterine fibroids.</li> </ul>	The following revisions to the clinical evidence were presented in the resubmission: <ul style="list-style-type: none"> <li>Data on real world practice study PREMYA (n=1473): patient assessed outcomes and CGI improvement.</li> <li>Additional Week 38 data on surgical outcomes from PEARL I</li> <li>Updated PSUR.</li> </ul>
Key efficacy data	<u>PEARL I: ulipristal* versus placebo</u> <ul style="list-style-type: none"> <li>Absolute difference in PBA chart score &lt;75 at Week 13: 72.7% (55.1%, 83.2%);</li> <li>Absolute difference in % change in total fibroid volume (cm<sup>3</sup>) from screening to Week 13: -22.6% (-36.1%, -8.2%).</li> </ul> <u>PEARL II: ulipristal* versus leuprorelin</u> <ul style="list-style-type: none"> <li>Absolute difference in PBA chart score &lt;75 at Week 13 (ITT): 3.1% (-6.9%, NR). Non-inferiority supported at a margin of -20%;</li> <li>Absolute difference in % change in total volume (cm<sup>3</sup>) of 3 largest fibroids from screening to Week 13 (ITT): <b>0.095 (0.005, 0.186)</b>;</li> <li>Absolute difference in % uterine volume (cm<sup>3</sup>) from screening to Week 13 (ITT): <b>0.161 (0.091, 0.232)</b>.</li> </ul>	Direct comparison: PEARL I - ulipristal* versus placebo. The results for these outcomes remain unchanged.
Key safety data	<u>PEARL I: ulipristal* versus placebo</u> The 95% confidence intervals overlapped 0 for all TEAEs occurring in at least 3% of the study population. <u>PEARL II: ulipristal* versus leuprorelin</u> Patients in the leuprorelin group had, on average, a significantly greater reduction in serum oestradiol levels compared to those receiving ulipristal 5 mg daily. Consistent with this finding, moderate to severe hot flushes were significantly less common with ulipristal 5 mg daily than with leuprorelin.	Direct comparison: PEARL I - ulipristal* versus placebo. The results remain unchanged PSUR: Updated PSUR data provided.
Clinical claim	"Qualitatively" non-inferior in terms of comparative effectiveness and "qualitatively" superior in terms of comparative safety over goserelin (with or without	Ulipristal is superior to placebo for the treatment of moderate to severe symptoms of uterine fibroids prior to planned surgery and

	July 2016 submission	Resubmission
	tibolone). <b>PBAC comment:</b> Clinical claim was not accepted. The claim for effectiveness was not supported by the data with a lack of evidence (paragraph 6.37). The claim for safety was not adequately supported by the data (paragraph 6.38).	has a comparable safety profile.
Economic analysis	Cost-minimisation analysis <b>PBAC comment:</b> A cost-minimisation approach versus goserelin was not appropriate given that goserelin is not listed on the PBS for this indication (paragraph 6.41). A cost utility analysis versus no treatment would be more appropriate (paragraph 7.8).	Cost utility analysis for the comparison of ulipristal and placebo presented in the resubmission (ICER = less than \$15,000 per QALY).
Estimated net cost to government	For the short-term surgery population without cost offsets for goserelin: Year 1: less than \$10 million, Year 5: less than \$10 million. <b>PBAC comment:</b> In line with the DUSC's comment, due to limited epidemiological evidence available, the estimated cost is highly uncertain. An incidence approach accounting for a prevalent patient population in Year 1 may be more appropriate. The estimates should exclude cost offsets for goserelin (paragraph 7.9).	Cost offsets for goserelin were removed. An allowance for prevalent patients was included in Year 1 in line with the DUSC advice. Year 1: less than \$10 million; Year 5: less than \$10 million. A Risk Share Arrangement was proposed to account for residual uncertainty surrounding cost to the government.
PBAC outcome	Rejected on the basis that the clinical place in therapy was not established, use of the nominated comparator goserelin in clinical practice was not substantiated and it was not PBS listed, comparative effectiveness and safety of ulipristal to goserelin not established, surgical outcomes impact not presented.	To be decided.

\* As the recommended dose for ulipristal is 5 mg daily, the 10 mg ulipristal treatment arm was not presented in the commentary.

PBA = pictorial blood-loss assessment; TEAE = treatment emergent adverse event; RCT = randomised controlled trial; CGI = clinical global assessment

Paragraph references refer to the July 2016 ulipristal Public Summary Document.

#### 4 Clinical place for the proposed therapy

- 4.1 Uterine fibroids are common benign neoplasms of the uterus. They are oestrogen dependent and exhibit maximal growth during the decade before menopause and decrease in size thereafter. Uterine fibroids are frequently asymptomatic, but can cause heavy or prolonged menstrual bleeding and resultant anaemia, dysmenorrhea, pelvic pressure, pain and bulk or pressure symptoms.
- 4.2 Ulipristal is a selective progesterone receptor modulator. The resubmission proposed ulipristal for short-term use (3 months) in patients eligible for and planning surgery, as a means of stabilising symptoms and potentially facilitating less invasive surgical techniques.
- 4.3 The PBAC received advice from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) in July 2016. They indicated that a three-month course of ulipristal has a possible clinical place as an oral alternative to gonadotropin-releasing hormone (GnRH) analogues to reduce size of uterine fibroids

prior to surgery. The College also considered repeated 3 month courses of ulipristal may have a role in the long term management of fibroids, noting

- Monitoring of endometrial thickness (ultrasound) and possibly histology (biopsy) is required until there is good evidence that these changes do not eventually predispose to malignancy.
- It is not yet clear whether there is a long term benefit of one or two courses of ulipristal in a majority of women. It is possible that a significant number of women would require repeated courses of ulipristal to maintain symptomatic relief.
- More long term data on side effect profile and efficacy are required before long term use can be recommended outside the context of a large randomised controlled trial.

- 4.4 In July 2016, the PBAC agreed there was a possible clinical place for ulipristal in short-term therapy prior to surgery (paragraph 7.5 of the July 2016 ulipristal Public Summary Document (PSD)).

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

## **5 Comparator**

- 5.1 The resubmission nominated placebo (no treatment) prior to planned surgery as the main comparator. While the July 2016 submission nominated goserelin as the main comparator, the PBAC considered that a resubmission would need to include no treatment as a comparator (paragraph 7.10 of the July 2016 ulipristal PSD). The ESC noted the comparison presented in the resubmission was 3 months of ulipristal followed by surgery with 3 months of placebo followed by surgery (rather than with immediate surgery), and the benefits claimed for ulipristal related to reduced symptoms for the 3 months prior to surgery as well as facilitating less invasive surgery.
- 5.2 The ESC noted that although placebo is the appropriate comparator, in clinical practice patients would receive treatments aimed at controlling menstrual bleeding. Conservative management may include treatments such as tranexamic acid, nonsteroidal anti-inflammatory (NSAI) drug, oral contraceptive pills and intrauterine devices (IUDs). These alternatives were not utilised in the trial, however, may be relevant when considering the impact of ulipristal in comparison to current practice. The pre-PBAC response stated that NSAI medicines were used by approximately 8% of subjects during the clinical trial. Additionally, although conservative management in clinical practice may include use of tranexamic and/or oral or intrauterine contraceptives, these alternatives are respectively limited by significant safety, efficacy and practical issues. The sponsor stated there are no robust data available which inform the effectiveness and safety of these treatments, either in comparison to or combination with ulipristal, in the target indication.
- 5.3 The ESC noted that hysterectomy rates in Australia have declined substantially over time, and the use of PBS medications that may control uterine bleeding appears to have been increasing, although, these medications can be prescribed for other purposes (Yusuf et al., 2016). Overall, the current management of symptomatic

uterine fibroids in Australian clinical practice is unclear and is likely to vary based on patient preferences and location, as well as clinical factors.

- 5.4 Given the economic model included benefits associated with reduced symptoms whilst waiting for surgery as well as less invasive surgery, the PBAC considered the appropriate comparison would be ulipristal plus conservative management versus placebo plus conservative management.

*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 that no consumer comments were received for this item.

### ***Clinical trials***

- 6.3 The resubmission was based on:
- one head-to-head trial (PEARL I) comparing ulipristal 5 mg once per day (n=96) to placebo (n=48),
  - one supportive trial (PEARL II) comparing ulipristal 5 mg once per day (n=102) to leuprorelin (n=102), and
  - one supportive real-world practice study (PREMYA).
- The PEARL I and PEARL II trials were included in the July 2016 submission. As for the July 2016 submission, since the recommended dose of ulipristal in Australia is 5 mg once daily, the results for the 10 mg treatment groups are not presented
- 6.4 Details of the trials presented in the resubmission are provided in Table 2.

**Table 2: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Key trial: Ulipristal versus placebo</b>		
PEARL I (PGL07-021)	A phase III, randomised, parallel group, double-blind, placebo-controlled, multi-centre study to assess the efficacy and safety of ulipristal acetate versus placebo for pre-operative treatment of symptomatic uterine myomas.  Donnez J, Tatarчук TF, <i>et al.</i> Ulipristal acetate versus placebo for fibroid treatment before surgery.	September 2010.  <i>New England Journal of Medicine</i> 2012; 366 (5):409-20.
<b>Supportive trials and studies</b>		
PEARL II (PGL07-022)	A phase III, randomised, parallel group, double-blind, double-dummy, active comparator-controlled, multi-centre study to assess the efficacy and safety of ulipristal acetate versus GnRH-agonist (leuprorelin 3.75 mg) for pre-operative treatment of symptomatic uterine myomas.  Donnez J, Tomaszewski J, <i>et al.</i> Ulipristal acetate versus leuprolide acetate for uterine fibroids.	September 2010.  <i>New England Journal of Medicine</i> 2012; 366 (5):421-32.
PREMYA (PGL10-014)	A prospective multi-centre non-interventional study of women treated with Esmya® (ulipristal acetate) as pre-operative treatment of moderate to severe symptoms of uterine fibroids.	May 2016. Internal study publication.

Source: Table B-4, p24 of the resubmission

- 6.5 The key features of the comparative and non-comparative studies of ulipristal presented in the resubmission are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	Design/ duration	Risk of bias	Patient population	Outcomes
PEARL I	RCT comparing ulipristal 5 mg (n=96) and ulipristal 10 mg (n=98) with placebo (n=48), 3 months	Low	Pre-menopausal women with moderate to severe symptoms of uterine fibroids who were planning surgery	<ol style="list-style-type: none"> <li>1) Percentage of patients with reduction of uterine bleeding at Week 13, defined as a PBA chart score of less than 75</li> <li>2) Change in total fibroid volume from screening to Week 13, assessed by MRI</li> <li>3) Reduction in uterine volume from screening to Week 13, assessed by MRI</li> <li>4) Changes in haemoglobin, haematocrit, and ferritin levels</li> <li>5) SF-MPQ</li> <li>6) MDUFQ</li> <li>7) Surgical outcomes</li> </ol>
PEARL II	Non-inferiority RCT comparing ulipristal 5 mg (n=102) and ulipristal 10 mg (n=103) with leuprorelin (n=102), 3 months	Low	As above	<ol style="list-style-type: none"> <li>1) Proportion of patients with reduction of uterine bleeding at Week 13, defined as above</li> <li>2) Change in uterine volume from baseline to Week 13</li> <li>3) Change in volume of the 3 largest fibroids from baseline to Week 13</li> <li>4) Change in haemoglobin, haematocrit and ferritin levels</li> <li>5) SF-MPQ</li> <li>6) UFS-AOL</li> </ol>
PREMYA	Non-comparative real-world study (n=1,473), 15 months follow-up	High	Pre-menopausal women with moderate to severe symptoms of uterine fibroids who were initiating treatment with ulipristal	<ol style="list-style-type: none"> <li>1) Patient treatment benefit</li> <li>2) UFS-AOL</li> <li>3) Clinical global impression – improvement</li> <li>4) VAS – pain</li> <li>5) Interventions post-ulipristal treatment</li> </ol>

MDUFQ = Measurement of discomfort due to uterine fibroids questionnaire; MRI = magnetic resonance imaging; PBA = pictorial blood-loss assessment; RCT = randomised controlled trial; SF-MPQ = Short-form McGill Pain questionnaire, UFS-QOL = uterine fibroid symptom and quality of life score; VAS = visual analogue scale  
 Source: Compiled during the evaluation

### **Comparative effectiveness**

6.6 The key primary and secondary outcome results of the PEARL I trial are presented in Table 4.

**Table 4: Key primary and secondary outcome results of the PEARL I trial**

	Ulipristal 5 mg N=95	Placebo N=48	Absolute difference (95% CI)	Relative risk <sup>^</sup> (95% CI)
<b>Primary outcomes</b>				
PBA chart score <75 at Week 13, n/N (%), ITT analysis (LOCF)				
LOCF	86/94 (91.5%)	9/48 (18.8%)	<b>72.7% (55.1%, 83.2%)</b>	<b>4.88 (2.70, 8.82)</b>
Observed	77/82 (93.9%)	7/36 (19.4%)	<b>74.0% (61.0%, 88.0%)<sup>^</sup></b>	<b>4.83 (2.48, 9.41)</b>
Change in total fibroid volume from screening to Week 13*, cm <sup>3</sup>				
% change, median (range) <sup>a</sup>	-21.2% (-41.2 to -1.1)	3.0% (-19.7 to 23.0)	<b>-22.6% (-36.1%, -8.2%)</b>	NA
<b>Secondary outcomes</b>				
Change in uterine volume from screening to Week 13, cm <sup>3</sup>				
% change, mean (SD)	-8.67% (34.4)	5.91% (20.1)		NA
Change, log <sub>10</sub> total volume (SE) <sup>b</sup>	-0.072 (0.015)	0.007 (0.019)	<b>-0.079 (-0.131, -0.028)</b>	NA
Change in haemoglobin from baseline to Week 13 (LOCF)				
Haemoglobin, g/dL, mean (SD)				
Baseline	9.32 (1.50)	9.55 (1.18)		
Week 13	13.50 (1.32)	12.61 (1.30)		
Mean change	4.25 (1.90)	3.10 (1.68)	<b>0.92 (0.39, 1.44)</b>	NA
Underwent surgery <sup>a</sup>	41 (43.2%)	19 (39.6%)	0.04 (-0.13, 0.21) <sup>^</sup>	1.09 (0.72, 1.66)
Laparotomic hysterectomy	11 (11.6%)	10 (20.8%)	-0.09 (-0.22, 0.04) <sup>^</sup>	0.56 (0.25, 1.22)
Vaginal/laparoscopic hysterectomy	7 (7.4%)	0 (0.0%)	<b>0.07 (0.01, 0.13)<sup>^</sup></b>	7.66 (0.45, 131.3)
Myomectomy	12 (12.6%)	5 (10.4%)	0.02 (-0.09, 0.13) <sup>^</sup>	1.21 (0.45, 3.24)
UAE	11 (11.6%)	4 (8.3%)	<b>0.12 (0.05, 0.19)<sup>^</sup></b>	11.74 (0.71, 195.1)

CI = confidence interval; ITT = intention to treat; LOCF = last observation carried forward; PBA = pictorial blood-loss assessment; SD = standard deviation; SE = standard error; UAE = uterine artery embolisation; LOCF -= last observation carried forward; NA = not applicable

<sup>a</sup> Source: Donnez *et al.* (2012). Results are presented based on the Week 38, ITT analysis.

<sup>b</sup> Source: Table 21, p107 PEARL I CSR

\* Total fibroid volume derived as the sum of the individual fibroid volumes

<sup>^</sup> Figures were estimated during the evaluation using RevMan 5.3

Figures in bold indicate statistically significant differences

While the trial also included results for ulipristal 10 mg, since the recommended dose for ulipristal is 5 mg daily, the 10 mg ulipristal treatment arm results are not presented

Source: Tables B-17, B-18, B-20, B-24 and B-25, pp41-45 of the resubmission.

- 6.7 The results indicated that, at week 13:
- a statistically significantly greater proportion of women treated with ulipristal achieved a pictorial blood-loss assessment chart (PBA-C) score of <75;
  - those treated with ulipristal achieved statistically significant (i) reductions in total fibroid and uterine volume, and (ii) increases in haemoglobin levels; and
  - there were no consistent statistically significant differences in the proportion of women who underwent surgery or the types of surgery undertaken.
- 6.8 There were no statistically significant differences in pain in terms of the change from baseline to week 13 as measured by the Short-form McGill Pain Questionnaire (SF-MPQ) Part A (main component of the questionnaire), Part B (VAS) or Part C (pain intensity) for ulipristal 5 mg compared to placebo in the ITT analysis. The pre-PBAC response argued that ulipristal was associated with a significant improvement from baseline with respect to SF-MPQ subscales, the UFS-QoL symptom severity and total scores, all individual EQ-5D domain scores and the EQ-5D VAS through the first cycle of therapy (13 weeks) in both the larger PEARL-III and PEARL-IV studies. It was also noted that these studies were not placebo controlled and included patients

receiving ulipristal 10 mg, however the sponsor considered the results to be relevant. The ESC and PBAC noted there were statistically significant differences across the treatment groups for the change from baseline to week 13 for the Measurement of discomfort due to uterine fibroids questionnaire (MDUFQ). The ESC and PBAC noted this questionnaire was developed by the sponsor, however no information regarding the validation of this questionnaire was provided.

- 6.9 As for the July 2016 submission, the resubmission provided Week 38 data on the surgical interventions planned and completed by treatment group for patients in the PEARL I trial. This analysis showed that fewer patients in the placebo group compared to the ulipristal group underwent surgery by Week 38, with 29/48 (60.4%) of the placebo treated patients and 52/95 (54.7%) of the ulipristal 5 mg treated patients having no surgery. This difference was not statistically significant. It is not clear why surgery was cancelled more often for placebo treated patients compared to ulipristal treated patients.
- 6.10 The resubmission stated that the results from PEARL I indicated that the proportion of patients whose completed surgery involved hysterectomy was lower for ulipristal treated patients compared to placebo treated patients. The resubmission's statement was technically correct, since based on surgeries completed, of the 19 patients who had surgery in the placebo group, 52.6% had hysterectomy and of the 41 patients who had surgery in the ulipristal 5 mg group, 43.9% had hysterectomy. Analyses conducted during the evaluation indicated that the difference in rates of hysterectomy were not statistically significant. In addition, since hysterectomy was actually planned more commonly for the placebo treated patients, differences in the baseline demographics may have partly accounted for this difference.
- 6.11 Additionally, the surgical outcome results were highly unreliable for the following reasons:
- They were exploratory endpoints;
  - The results were based on small sample sizes;
  - Long-term outcomes on patients who did not have surgery were not reported, thus the final rate of surgical interventions for both treatment groups was not able to be determined;
  - The Clinical Study Report noted a strong centre effect (p113) in surgical outcomes across study sites of the multi-national trial. This suggested that surgery rates may have had more to do with clinical decision making in the respective sites rather than be due to ulipristal treatment; and
  - The centre effect also demonstrated it was unlikely that these results would be directly applicable to the Australian treatment setting.
- The ESC noted that in practice the type of surgery performed would also depend on clinical factors such as where the fibroid was located on the uterus, clinician and patient preferences, and access/availability and this was not explored in the resubmission. The ESC also noted that the proposed listing was for patients with factors which would make surgery 'technically difficult' and that in these circumstances it was considered unlikely that a single course of ulipristal would significantly impact the type of surgery received.
- 6.12 Overall, the ESC and PBAC considered none of the evidence presented in the resubmission was sufficient to determine treatment-related differences in surgical outcomes, including the potential of ulipristal given pre-operatively for 3 months to

allow for the provision of less invasive surgical procedures. Nevertheless, the rates of surgical interventions completed in each treatment group from PEARL I formed the basis for the rates of surgical interventions for ulipristal and placebo in the economic evaluation. The ESC noted that to understand the clinical significance of the reductions in uterine volume observed with ulipristal, information regarding duration of procedures, complication rates, patient satisfaction with the outcome and costs would be required, however, this information is not available. Consequently, the PBAC agreed with the ESC that ulipristal's clinical benefit may be related to improving quality of life while waiting for surgery, rather than affecting the rate or type of surgeries performed.

- 6.13 The pre-PBAC response acknowledged the limitations of the exploratory analysis of surgical endpoints in the PEARL-I study, however noted that these are the only comparative randomised trial data available for these outcomes. The PSCR reiterates the sponsor's position that availability of a 3-month course of ulipristal is likely to shift the patterns of surgical intervention in real world clinical practice, resulting in increased use of less invasive, uterine sparing techniques in preference to abdominal hysterectomy, even if it is not possible to demonstrate this with any certainty, given available clinical data.
- 6.14 The ESC and PBAC noted the increase in haemoglobin in both the placebo and ulipristal arms of PEARL I, with the increase being statistically significantly greater in the ulipristal arm (Table 4). The increase in haemoglobin is likely to be at least in part due to high compliance with high doses of iron tablets (80 mg of iron supplementation (256.3 mg of ferrous sulphate)). The ESC considered this was unlikely to be reflective of clinical practice as women would unlikely be able to tolerate the high iron doses prescribed in the trial. The anaemia outcomes were not discussed in terms of relevance for the economic model.
- 6.15 Results for the PEARL II trial which compared ulipristal and leuprorelin, were evaluated as part of the July 2016 submission. The results were not re-evaluated for the resubmission because no new information was provided and the trial did not compare ulipristal to placebo (a brief summary of the results is provided in Table 1 above).
- 6.16 Results of the real-world non-comparative PREMYA study were not considered to provide any relevant information for the resubmission as patients enrolled in the study were not required to be planning surgery and the duration of treatment with ulipristal was not limited to 3 months.

### ***Comparative harms***

- 6.17 The key adverse events (AEs) in PEARL I are summarised in Table 5. The most frequent treatment-emergent AEs (TEAEs) in the ulipristal treatment arm were headache, and gastrointestinal AEs. Hot flushes were reported in 2.1% and 0% of patients in the ulipristal 5 mg and placebo groups respectively.

**Table 5: Summary of adverse events in the PEARL I (ulipristal versus placebo)**

PEARL I	Ulipristal 5 mg n (%) N=95	Placebo n (%) N=48	Absolute difference <sup>^</sup> (95% CI)
At least 1 AE	48 (50.5%)	24 (50.0%)	0.5% (-16.8%, 17.9%)
At least 1 TEAE	47 (49.5%)	22 (45.8%)	3.6% (-13.7%, 21.0%)
Drug-related TEAE	18 (18.9%)	4 (8.3%)	10.6% (-0.5%, 21.7%)
At least 1 Serious TEAE	2 (2.1%)	2 (4.2%)	-2.1% (-8.4%, 4.3%)
TEAE leading to discontinuation	1 (1.1%)	1 (2.1%)	-1.0% (-5.6%, 3.5%)
TEAE leading to study withdrawal	0	0	-
Serious TEAE in follow-up (Week 17-38)	0	1 (2.1%)	-2.1% (-6.1%, 2.0%)
<b>TEAEs occurring in at least 3% of the patients in any group</b>			
Headache	4 (4.2%)	2 (4.2%)	0.0% (-6.9%, 7.0%)
Constipation	4 (4.2%)	1 (2.1%)	2.0% (-3.6%, 7.8%)
Pyrexia	3 (3.2%)	2 (4.2%)	-1.0% (-7.7%, 5.6%)
Hypercholesterolaemia	3 (3.2%)	1 (2.1%)	1.1% (-4.3%, 6.4%)
Hypertriglyceridaemia	3 (3.2%)	1 (2.1%)	1.1% (-4.3%, 6.4%)
Nasopharyngitis	3 (3.2%)	0	3.2% (-0.4%, 6.7%)
Breast pain or tenderness	2 (2.1%)	0	2.1% (-0.8%, 5.0%)
Abdominal pain	2 (2.1%)	2 (4.2%)	-2.1% (-8.4%, 4.3%)
Hypothyroidism	2 (2.1%)	0	2.1% (-0.8%, 5.0%)
Influenza	1 (1.1%)	1 (2.1%)	-1.0% (-5.6%, 3.5%)
Dizziness	1 (1.1%)	0	1.1% (-1.0%, 3.1%)
Dysmenorrhoea	0	2 (4.2%)	-4.2% (-9.8%, 1.5%)

AE = adverse event; CI = confidence interval; TEAE = treatment-emergent AE

<sup>^</sup> Figures were calculated during the evaluation.

Source: Tables B-28 and B-29, pp48-49 of the resubmission; Table 3, p418 Donnez *et al* (2012)<sup>1</sup>

- 6.18 The resubmission presented the results from a retrospective analysis of a prospective database reported by Ferrero *et al* 2016 in its discussion on the extended assessment of comparative harms of ulipristal. The study suggested that 3-month preoperative treatment with ulipristal may increase the chance of complete myoma resection in patients with high complexity hysteroscopic myomectomy. However, given the retrospective, non-randomised nature of the study, any differences may not be solely attributable to ulipristal treatment.

### **Benefits/harms**

- 6.19 A summary of the comparative benefits for ulipristal 5 mg versus placebo (no treatment) is presented in Table 6.

<sup>1</sup> Donnez J, Tatarchuk TF, *et al*. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med*. 2012; 366 (5):409-20.

**Table 6: Summary of comparative benefits and harms for ulipristal and placebo**

Trial	Ulipristal	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)	
				Ulipristal	Placebo		
<b>Benefits</b>							
<b>PBA chart score &lt;75 at Week 13, n/N (%), ITT analysis<sup>a</sup></b>							
PEARL I	86/94	9/48	4.88 (2.70, 8.82) <sup>^</sup>	91.5	18.8	0.727 (0.551, 0.832)	
<b>% change in total fibroid volume from screening to Week 13 (cm<sup>3</sup>)<sup>b</sup></b>							
	Ulipristal			Placebo			Mean difference*: Ulipristal vs. placebo (95% CI)
	n	Mean $\Delta$ baseline	SD	N	Mean $\Delta$ baseline	SD	
PEARL I	95	142.5	133.3	48	136.0	191.4	-0.226 (-0.361,-0.082)

<sup>a</sup> Last observation carried forward.

<sup>b</sup> Change in total fibroid volume, defined as the sum of all the individual fibroid volumes: Median results.

<sup>^</sup> Figures were calculated during the evaluation. RD = risk difference; RR = relative risk.

Source: Compiled during the evaluation.

6.20 On the basis of direct evidence presented by the resubmission, the comparison of 13 weeks of treatment with ulipristal 5 mg once daily and placebo resulted in:

- A reduction in blood loss. For every 100 patients treated with ulipristal in comparison to placebo, approximately 73 additional patients would have a pictorial blood loss assessment (PBA) chart score of less than 75 (a score which is considered to be within the normal range of menstrual blood loss) at Week 13.
- A reduction in total fibroid and uterine volume. On average the reduction in total fibroid volume at 13 weeks is 22.6% greater with ulipristal compared with placebo. The resubmission did not indicate what difference in total fibroid volume was considered to be clinically meaningful.
- No statistically significant differences in the proportion of patients proceeding to surgery and no consistent differences in the types of surgeries performed. The ESC noted a difference in surgery did not form part of the clinical claim; however it was included in the economic model.
- A greater number of drug-related treatment emergent adverse events for patients treated with ulipristal (18.9%) compared to placebo (8.3%), although the difference was not statistically significant.

### **Clinical claim**

6.21 The resubmission described ulipristal as superior in terms of comparative effectiveness to placebo as a proxy for an equivalent period of conservative management, with an acceptable and comparable safety and tolerability profile.

- This claim was adequately supported in relation to effectiveness for controlling abnormal uterine bleeding and reducing both fibroid and uterine volume in pre-menopausal women eligible for surgery. This claim was accepted by the PBAC at the July 2016 PBAC meeting, and additional evidence available since this time did not counter this claim.
- The evidence presented in the resubmission indicated no statistically significant differences between ulipristal 5 mg and placebo with regard to surgery rates or types of surgery performed. Thus, there was insufficient data to indicate that ulipristal has the potential to facilitate less invasive surgical techniques.

- In relation to safety, although the differences were not statistically significant, there were numerically greater numbers of adverse events in the ulipristal group. The ESC considered there was insufficient data to support the claim that ulipristal is non-inferior to placebo in terms of comparative safety.
- 6.22 The PBAC considered the claim of superior comparative effectiveness of ulipristal over placebo was reasonable for the outcomes of controlling abnormal uterine bleeding and reducing both fibroid and uterine volume. The PBAC considered the claim of superior effectiveness was not adequately supported for the surgical or quality of life outcomes.
- 6.23 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

**Economic analysis**

- 6.24 The resubmission presented an economic model to evaluate the cost-effectiveness of ulipristal followed by surgery versus conservative management followed by surgery.
- 6.25 The summary of model structure and rationale is presented in Table 7. Regarding the model structure, the ESC considered the health states used within the model were treatment outcomes rather than health outcomes, and it was considered complicated given the available data. The ESC noted costs associated with conservative management for the treatment of symptoms were not included in the model.

**Table 7: Summary of model structure and rationale**

Time horizon	5 years in the model base case, based on 13-week PBA-C data from PEARL I.; and Week 13 and 38 surgical outcomes
Outcomes	QALYs
Methods used to generate results	Markov Cohort expected value analysis
Cycle length	13 weeks
Transition probabilities	Health states based on event – based transitions such as medical management, expectant management, surgical management, post non-invasive surgery, post-invasive surgery, death
Discount rate	5% for costs and outcomes
Software package	TreeAge 2016

Source: Constructed during the evaluation. PBA-C = pictorial blood-loss assessment chart

- 6.26 The two key drivers of the model were:
- differences in total QALYs in the first 13-week cycle of the model derived from (i) differences in rates of bleeding from the PEARL I trial, and (ii) utility values sourced from the literature.
  - differences in surgery rates for the types of surgeries performed and derived from PEARL I Part A and B surgery rates, despite these being non-statistically significantly different.

**Table 8: Key drivers of the model**

Description	Method/Value	Impact
Surgical outcomes	Modeled differences in proportion of patients proceeding to surgery; and differences in types of less and more invasive surgeries.	High, favoured ulipristal
Utility values for controlled and uncontrolled bleeding	0.73 for controlled bleeding, and 0.55 for uncontrolled bleeding, based on Hux 2015.	High, favoured ulipristal
Time horizon	5 years	High, favoured ulipristal

Source: Compiled during the evaluation

- 6.27 The PBAC considered no new convincing evidence was provided in the resubmission to alter its previous view that “there was no comparative evidence for the effectiveness of a single course of ulipristal in terms of surgical outcomes, including the potential to facilitate less invasive surgical techniques” (Ulipristal July 2016 PSD, paragraph 6.33).
- 6.28 The resubmission did not adequately address how improvements in controlling bleeding would translate to utility gains in a cost-utility model, and there was a high risk that the utility gains were overestimated.
- 6.29 The utility values used in the economic evaluation are summarised in Table 9.

**Table 9: Utility values used in the economic evaluation**

State	Value	Source:	Description
Medical health states			
Controlled bleeding	0.73	Hux 2015	<ul style="list-style-type: none"> <li>•Community values (i.e. general public as responders, not patients)</li> <li>•Canadian population</li> <li>•Descriptions based on focus groups and made to align with EQ-5D</li> </ul>
Uncontrolled bleeding	0.55		
Surgery health states			
Surgery	0.65	Nagy 2014	Estimation of EQ-5D utilities of hysterectomy and myomectomy using UFS-QOL responses in PEARL I by Rowen & Brazier 2011 (no further detail presented).
Complications (utility decrement)			
Major	-0.013	Hirst 2008	The authors assumed that major or severe complications would result in a utility decrement of 0.16 from the utility of successful procedure over a period of 28 days. Similarly, a utility decrement of 0.08 over a period of 14 days was applied to those who experienced minor complications.
Minor	-0.003		
Post-surgery health states			
Post-Surgery	0.81	Hawthorne 2013	Population norms for the AqoL derived from the 2007 Australian National Survey of Mental Health and Wellbeing, based on the assumption that post-surgery utilities would be the same as those of the general population.

- 6.30 The PBAC agreed with the ESC that it was unclear whether the utilities applied to the controlled and uncontrolled bleeding health states in the base case presented in the resubmission were relevant to how the health states were defined in the model (i.e. PBA-C score of <75 and ≥75 for controlled and uncontrolled bleeding, respectively). The ESC further noted the relatively large difference in the utility values for the

bleeding health states is inconsistent with the non-significant differences observed in PEARL I for the SF-MPQ.

- 6.31 Regarding the utility value for the surgery health state, the ESC and PBAC noted the same value was applied regardless of the type of surgery received.
- 6.32 Regarding the utility value for the post-surgery health state (0.81), the ESC and PBAC noted that this was substantially higher than for the controlled bleeding health state (0.73) and that it may have been more appropriate to use the 0.73 value for post-surgery state.
- 6.33 Table 10 presents the results of the economic evaluation.

**Table 10: Results of the economic evaluation**

Component	Ulipristal	Conservative management	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/extra QALY gained</b>			<b>\$ [REDACTED]</b>

Source: Table D.11, p97 of the resubmission

- 6.34 The PSCR acknowledged the error in the economic model identified during the evaluation where the rate of minor complications was applied to the sub-state of major complications and vice versa. The corrected base case ICER was slightly lower (less than \$15,000 per QALY) than that presented in the resubmission (less than \$15,000 per QALY). The base case ICER was not revised during the evaluation because of the small difference.
- 6.35 Removing surgeries from the model is consistent with no differences in surgical outcomes. It was acknowledged in the PSCR that there are clear limitations in the available clinical data describing the impact of ulipristal treatment on surgical outcomes and how these can be applied to an economic evaluation. However the sponsor does not believe these limitations are sufficient to warrant simply ignoring this potential treatment effect and removing surgery from the structure of the model. It was suggested in the PSCR that the uncertainty could be better assessed via other, less restrictive sensitivity analyses. The ESC and PBAC considered that there was insufficient clinical data to support inclusion of surgical outcomes in the base case economic evaluation.
- 6.36 Table 11 presents the results of the economic evaluation only considering the first 13 weeks of the model i.e., with consideration of surgery removed. Using the utilities nominated by the resubmission and assuming that the transition from the 'uncontrolled' to 'controlled' bleeding state occurs at the beginning of the first 13-week cycle results in a significantly increased ICER (\$15,000/QALY - \$45,000/QALY compared with less than \$15,000 per QALY for the submission's base case).

**Table 11: Results of select sensitivity analyses on 13-week model**

Analyses	Incremental costs	Incremental QALYs	ICER
Assuming transition to “controlled” bleeding occurs at the beginning of the first 13-week cycle			
13 week horizon scenario	\$█	█	\$█
13 weeks & Nagy 2014 utilities (0.72 & 0.83)	\$█	█	\$█
13 weeks & O’Sullivan 2009 utilities (0.67 & 0.76)	\$█	█	\$█

ICER = incremental cost-effectiveness ratio

- The redacted table shows ICERs in the range of \$15,000/QALY - \$75,000/QALY.
- 6.37 The ESC noted the ICER was sensitive to the utility values used. Use of the alternative utility values presented in the resubmission in the 13-week model increased the ICER to up to \$45,000/QALY - \$75,000/QALY gained. The PSCR argued that the utility values from Hux 2015 were the most robust and appropriate of the values identified. It was noted the values in Nagy 2014 were obtained by expert opinion, and lacked rigour and applicability compared with those reported by Hux 2015. The values used in O’Sullivan 2009 and Babashov 2015 were noted to be based on unpublished data, with unclear analytical methods, from a clinical trial of Magnetic Resonance Guided Focused Ultrasound (MRgFUS) rather than medical management. It was further noted that use of other alternative utility values identified in the submission, but not cited in the commentary, reduced the ICER to less than \$15,000 per QALY.
- 6.38 The sponsor considered the 13-week model represents an extremely conservative approach with respect to valuing the clinical benefits of pre-surgical ulipristal treatment. However, in the pre-PBAC response the sponsor presented a 13-week analysis using the EQ-5D VAS scores for pre-treatment (0.744) and post-treatment (0.843) with ulipristal 5 mg in the PEARL-IV study as proxy utility weights for controlled and uncontrolled bleeding. The resulting ICER was \$15,000/QALY - \$45,000/QALY gained. The sponsor proposed reducing the requested DPMQ by █%, to \$█ per pack (\$█ per course) to reduce the ICER to \$15,000/QALY to \$45,000/QALY.
- 6.39 The ESC noted the model applied the improvement in quality of life associated with controlled bleeding from the first day of treatment and this was maintained for the 13 weeks. Assuming transition to “controlled” bleeding occurs in the middle of the first 13-week cycle (at 6.5 weeks) increased the ICER from \$15,000/QALY - \$45,000/QALY to \$45,000/QALY - \$75,000/QALY. This approach is equivalent to using a mid-cycle correction technique as described by Naimark et al. (2008). The pre-PBAC noted the model applies the assumed improvement in quality of life from the first day of treatment, but also abruptly truncates any clinical effect at the end of 13 weeks even though there is evidence that indicates that bleeding and bulk symptoms, and health related quality of life revert only gradually following cessation of treatment. The PBAC considered it reasonable to assume a quality of life benefit for the entire 13 week duration of the model noting that the full benefit would not be realised from day 1 but also that the benefit extends beyond 13 weeks.

**Drug cost/patient/course: \$ [REDACTED] (based on revised price requested in the pre-PBAC response)**

6.40 The drug cost/patient/course was based on one 3-month cycle of treatment per patient per course, with the resubmission proposing restricting use of ulipristal to one course every 18 months.

**Estimated PBS usage & financial implications**

6.41 This re-submission was considered by DUSC.

**Table 12: Estimated number of patients to be treated and packs to be dispensed**

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients eligible for pre-surgery management with ulipristal	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Appropriate for short term treatment (July 2016 submission)**	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Uptake rate: public hospital patients	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
Uptake rate: private hospital patients	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
Overall uptake rate based on 42.4/57.6 split of public to private patients	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
Uptake rate July 2016	10%	20%	30%	40%	50%
Estimated number of patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number treated – July 2016**	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Packs of ulipristal dispensed per year***	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Source: Table E.2.2 7.08.COM.50. Amended in DUSC Advice.

\* Corrected in DUSC Advice to apply additional 15% for the prevalent pool to public hospital patients only instead of to the whole eligible population. This aligns with the submission text (p100).

\*\* Patients treated from the July 2016 submission were for the pre-surgery acute state.

\*\*\* Assuming three prescriptions per patient.

The redacted table shows that at year 5, the estimated number of patients treated was 10,000 – 50,000, and the estimated number of packs dispensed was 10,000 – 50,000.

6.42 The PBAC agreed with the DUSC and considered the financial estimates highly uncertain and may be underestimated. In particular:

- There was a high degree of uncertainty regarding the number of patients who would be eligible for ulipristal under the proposed restriction. The DUSC noted that no clear basis was provided for the chosen proportion of procedures that were for uterine fibroids. Calibration of these proportions to the procedure mix in the PEARL I trial did not reduce uncertainty given that the procedure mix in PEARL II differed greatly from PEARL I. The re-submission’s approach using the PEARL I trial for calibration led to a higher estimate of patient numbers.
- The resubmission made a 15% prevalence adjustment to the number of patients undergoing surgery in Year 1. The pre-PBAC response confirmed the DUSC correction that the prevalence adjustment was intended to be applied to public hospital patients only but was applied to the whole eligible population. The PBAC noted that no justification was provided in the resubmission regarding the prevalence adjustment being 15%.
- While the uptake rate was also appropriately higher than that used in the July 2016 submission, in-line with the DUSC advice for the July 2016 PBAC meeting

(5.14.DUSC ADV.1), there was still uncertainty surrounding the treated patient population. It is possible that the uptake rate in the private hospital system would be higher than anticipated. The DUSC noted that it is unclear how clinician and patient preference might change if ulipristal were subsidised; it could become standard pre-surgery practice if there is a perception of reduced surgical morbidity. The pre-PBAC response argued that clinical experts working in the private sector suggested ulipristal is unlikely to be widely prescribed in order to delay or prevent surgery, but will typically be reserved for cases where debulking of the fibroids is clearly indicated to facilitate less invasive surgery and/or improve patient outcomes.

- The DUSC noted that the requested restriction permits treatment more than once in a lifetime. Given that the financial estimates did not account for patients who do not proceed with planned surgery and are re-treated with ulipristal, the DUSC considered that women potentially using ulipristal more than once in a lifetime were not accounted for in assessing cost effectiveness and financial costs. The pre-PBAC response argued that evidence from across the ulipristal clinical development program indicates that symptoms of uterine fibroids are likely to relapse to baseline levels within a few months of completing a single course of ulipristal. Hence the highly intermittent regimen suggested by DUSC is neither clinically appropriate nor likely to emerge in practice. The pre-PBAC response further noted that the proposed 18-month interval is reasonably arbitrary, and represents a pragmatic limitation considered sufficient to discourage de facto use as a long-term intermittent regimen while not excluding treatment of the significant proportion of patients who experience a recurrence of their fibroids following surgery or surgical substitute interventions.
- The cost-offsets expected due to less intensive surgical procedures were not supported by the available evidence and may not be realised (Table 13).

Table 13: Estimated net cost

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS	\$ [redacted]*	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to PBS July 2016	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to MBS	-\$ [redacted]*	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]
Net cost to MBS July 2016	-	-	-	-	-
<b>Net cost PBS/MBS</b>	\$ [redacted]*	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost PBS/MBS July 2016	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Source: 7.08.COM.13, Table 10.

\*Amended in DUSC Advice to correct application of prevalent pool (see Table 12).

The redacted table shows that at year 5, the estimated net cost to the PBS was less than \$10 million per year.

- 6.43 The results of the univariate sensitivity analysis presented in the re-submission indicated that the 5-year cost of ulipristal to the government would increase from \$30 - \$60 million in the base case, to \$30 - \$60 million if utilisation in private hospitals was the same as public hospitals and to \$30 - \$60 million assuming the number of patients undergoing UAE/EA and hysterectomy for uterine fibroids was [redacted]%, rather than [redacted]% and [redacted]% as estimated by the resubmission.

**Table 14: Updated sensitivity analyses**

Analysis	Base Case	Worst Case		Best Case	
	Value	Value	Net cost*	Value	Net cost*
Base case*	\$ [REDACTED]				
Procedures due to fibroids					
Non-invasive (UAE/EA)	27.5%	40.0%	\$ [REDACTED]	[REDACTED]%	\$ [REDACTED]
Myomectomy	[REDACTED]%	[REDACTED]%		[REDACTED]%	
Hysterectomy	25.5%	40.0%		[REDACTED]%	
Uptake of ulipristal					
Public	[REDACTED]%	[REDACTED]%	\$ [REDACTED]	[REDACTED]%	\$ [REDACTED]
Private	[REDACTED]%	[REDACTED]%		[REDACTED]%	
Future procedures mix					
As Non-invasive	[REDACTED]%	[REDACTED]%	\$ [REDACTED]	[REDACTED]%	\$ [REDACTED]
As Myomectomy	[REDACTED]%	[REDACTED]%		[REDACTED]%	
As Non-invasive	[REDACTED]%	[REDACTED]%		[REDACTED]%	

Source: Table E-10 re-submission p111.

\* Amended in DUSC Advice to correct application of prevalent pool (see Table 12).

The redacted table shows best case net costs in the range of \$10 - \$60 million, and worst case net costs in the range of \$30 - \$60 million.

### Quality Use of Medicines

6.44 The resubmission suggested that some sub-optimal alternatives (such as goserelin and leuprorelin) are currently used for patients with uterine fibroids who are planning surgery and that these have recognised safety issues and limited clinical effectiveness. With a PBS listing for ulipristal, the resubmission suggested that this would lead to less invasive surgical interventions and less use of sub-optimal alternatives, resulting in more efficient use of resources. These assertions were not supported by the evidence presented in the resubmission.

### Financial Management – Risk Sharing Arrangements

6.45 Due to the uncertainty surrounding the financial estimates and in line with the advice from the PBAC for the July 2016 submission (Ulipristal PSD, July 2016, paragraph 6.45) the resubmission proposed a Risk Share Arrangement (RSA). The RSA was amended in the PSCR to be that if utilisation exceeds finally agreed estimates by any more than [REDACTED]% in any of the first [REDACTED] years of listing, the sponsor would repay [REDACTED]% of the net cost to the Australian Government of the difference between actual and predicted expenditure at the end of each year this occurs. The PBAC agreed with DUSC that the proposed risk share arrangement is not sufficient to manage the extent of uncertainty associated with the cost effectiveness of ulipristal.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

## 7 PBAC Outcome

7.1 The PBAC did not recommend the listing of ulipristal on the PBS for the treatment of

moderate to severe symptoms of uterine fibroids prior to planned surgery on the basis that the clinical place in therapy was unclear due to the impact of treatment on surgical outcomes versus placebo (no treatment) being unknown and the benefits in terms of symptom control compared with currently used alternatives not being assessed.

- 7.2 The PBAC considered the proposed restriction did not clearly identify the patients likely to benefit from treatment with ulipristal and agreed with DUSC that it is unclear how clinician and patient preference might change if ulipristal was subsidised. The pre-PBAC response argued that clinical experts working in the private sector suggested ulipristal is unlikely to be widely prescribed in order to delay or prevent surgery, but will typically be reserved for cases where debulking of the fibroids is clearly indicated to facilitate less invasive surgery and/or improve patient outcomes. The PBAC considered there is a risk that ulipristal would be used routinely prior to surgery in patients with uterine fibroids and considered this inappropriate given the lack of evidence demonstrating an impact on surgical outcomes.
- 7.3 The PBAC noted the issues raised by ESC and DUSC relating to restricting treatment to three months within an 18 month period, and the comments included in the pre-PBAC response that a single three month course is consistent with the available clinical data, and will generally provide four to six months relief from moderate to severe symptoms of fibroids. The PBAC noted the proposed 18 month period was arbitrarily selected and that RANZCOG considered repeated three month courses may have a role in the long-term management of fibroids and retreatment is not precluded in the ulipristal Product Information.
- 7.4 The PBAC noted the resubmission nominated placebo (no treatment) prior to planned surgery as the main comparator, and this was considered in the resubmission to be consistent with the PBAC's advice for the July 2016 submission. The PBAC also noted the benefits claimed in the resubmission related to (i) facilitating less invasive surgery and (ii) reducing symptoms in the 3 month period prior to surgery. For the benefit relating to surgery the PBAC reiterated its previous advice that placebo is the appropriate comparator. In terms of reducing symptoms the PBAC noted that alternative treatments such as tranexamic acid, nonsteroidal anti-inflammatory (NSAI) drug, oral contraceptive pills and intrauterine devices (IUDs) are used in the clinical practice and should be considered. The PBAC considered the substantial reduction in hysterectomy rates over time suggests that treatment practices have changed and there are effective alternatives to surgery for patients with uterine fibroids. The PBAC considered the appropriate comparison would be ulipristal plus conservative management versus placebo plus conservative management.
- 7.5 The PBAC recalled that ulipristal is effective at controlling uterine bleeding and reducing fibroid and uterine volume, and increasing haemoglobin levels. It was noted that fibroids can have physical effects due to their size and hence a reduction in symptoms could be expected due to the reduction in the size of the fibroids. However, the PBAC noted the data supporting a reduction in symptoms and improved quality of life from the PEARL I trial were limited with no statistically significant differences in pain from baseline to week 13 based on the Short-form McGill Pain Questionnaire. Although there were statistically significant differences across the treatment groups for the Measure of Discomfort due to Uterine Fibroids

Questionnaire (MDUFQ) the PBAC noted the ESC's concern regarding the lack of formal validation of the questionnaire.

- 7.6 The PBAC noted the resubmission included additional data on surgical outcomes from the PEARL I trial. The PBAC noted that there were no statistically significant differences in the proportion of patients receiving surgery or types of surgery performed, and it was unclear why surgery was cancelled more often for placebo treated patients compared with ulipristal treated patients. The PBAC agreed with ESC that the type of surgery performed would depend on clinical factors such as where the fibroid was located on the uterus, clinician and patient preferences, and access/availability, and possibly related to this noted the difference in surgery rates across the trial centres. The PBAC further agreed with ESC that to understand the clinical significance of the reductions in uterine volume observed with ulipristal, information regarding duration of procedures, complication rates, patient satisfaction with the outcome and costs would be required.
- 7.7 Overall, the PBAC considered the claim of superior comparative effectiveness of ulipristal over placebo was reasonable for the outcomes of controlling abnormal uterine bleeding and reducing both fibroid and uterine volume. The PBAC considered the claim of superior effectiveness was not adequately supported for the surgical or quality of life outcomes.
- 7.8 The PBAC noted treatment related adverse events that were considered to be drug related were more frequent in the ulipristal arm (18.9%) compared with the placebo arm (8.3%) of PEARL I, although the difference was not statistically significant. Overall, the claim of non-inferior comparative safety was considered by the PBAC to not be adequately supported by the data.
- 7.9 The PBAC considered including surgical outcomes in the base case of the economic model was not reasonable as there were no consistent statistically significant differences in the proportion of women who underwent surgery or the types of surgery undertaken demonstrated in the PEARL I trial. The PBAC noted removing surgical outcomes from the model increased the ICER substantially from less than \$15,000 per QALY to \$15,000 - \$45,000 per QALY gained.
- 7.10 The PBAC discussed that the results of the 13 week model with surgical outcomes removed was very sensitive to the utility values used for the controlled and uncontrolled bleeding health states. The PBAC noted the utility values used in the resubmission of 0.73 and 0.55, respectively, resulted in an ICER of \$15,000 - \$45,000 per QALY gained whereas the utility values presented in the pre-PBAC response (0.843 and 0.744) resulted in an ICER of \$15,000 - \$45,000 per QALY gained with a ■■■% reduction in the dispensed price for ulipristal.
- 7.11 The PBAC noted the ESC presented alternative scenarios assuming the transition to controlled bleeding occurs in the middle of the first 13-week cycle (at 6.5 weeks). The PBAC considered it reasonable to assume a quality of life benefit for the entire 13 week duration of the model noting that the full benefit would not be realised from day 1 but also that the benefit extends beyond 13 weeks.
- 7.12 The PBAC considered the value of the analysis based on the 13 week model was limited because alternative treatments to reduce the symptoms associated with

fibroids were not considered and the resubmission did not adequately address how improvements in controlling bleeding would translate to utility gains.

- 7.13 The PBAC considered the financial estimates were highly uncertain and likely to be underestimated. The PBAC noted that there was no clear basis for the chosen proportion of the procedures that were for uterine fibroids, for the magnitude of the 15% prevalence adjustment in year 1 or for the assumed uptake rates. It was further noted that the financial estimates did not account for patients who are re-treated with ulipristal and the estimated cost offsets associated with a reduction in surgery may not be fully realised given the uncertain impact of ulipristal on surgical outcomes.
- 7.14 The PBAC considered that any resubmission should be a major submission with the clinical place and benefits of ulipristal clearly defined compared with the treatments currently utilised in clinical practice.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

Ulipristal (5 mg tablets) is a rapidly emerging standard of care for treatment of moderate to severe uterine fibroids, in both short-term pre-surgical and longer-term intermittent treatment settings, and is now widely reimbursed for such use across Europe.

Vifor Pharma is therefore greatly disappointed with the PBAC's decision to reject Ulipristal for a second time, and unclear as to how PBS listing could realistically be achieved, given existing, planned and practically feasible clinical trials.

Notwithstanding this, Vifor remains committed to ensuring this important medicine is made available in some way to Australian patients with moderate to severe symptoms of uterine fibroids, and will continue to work towards this aim.