

**5.14 ULIPRISTAL ACETATE,
TABLET, 5 MG,
ESMYA®, VIFOR AUSTRALIA PTY LTD.**

1 Purpose of Application

- 1.1 The submission requested a Section 85, Authority Required (Streamlined) listing for ulipristal for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

2 Requested listing

- 2.1 The listing proposed in the submission was based on the clinical setting of both short and long-term management of moderate to severe symptoms of uterine fibroids. The sponsor requested in the Pre-PBAC response to withdraw the long-term treatment setting, narrowing the proposed listing to short-term therapy prior to planned surgery.

2.2 The requested listing as updated in the Pre-PBAC request is presented below.

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Moderate to severe
Condition:	Uterine fibroids
PBS Indication:	Management of moderate to severe symptoms uterine fibroids prior to planned surgery.
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by, or under the direction of, a gynaecologist
Clinical criteria:	Patient must not be receiving concomitant treatment with a gonadotropin releasing hormone analogue. Patient must have significant bleeding/anaemia, or Patient must have large and/or multiple fibroids, or Patient must have other factors which would make surgery technically difficult
Population criteria:	Patient must be an adult female of reproductive age The patient must be eligible for and planning surgery for uterine fibroids
Prescriber Instructions	No increase in the maximum quantity or number of repeats may be authorised. No more than one three-month cycle of therapy will be authorised within 18 months. No increase in the maximum quantity or number of repeats may be authorised.

* Dispensed price for maximum quantity (DPMQ) as reported in the submission. The submission used a DPMQ of \$ [REDACTED] in the economic and financial analyses.

2.3 The proposed PBS listing was consistent with the approved TGA indication.

2.4 The submission was based on a cost-minimisation analysis of ulipristal compared with goserelin (a gonadotrophin releasing hormone (GnRH) analogue), either alone or in conjunction with hormonal add-back therapy (tibolone). Goserelin was not listed on the PBS for the treatment of symptoms of uterine fibroids at the time of the PBAC consideration. The cost-effectiveness of goserelin in the treatment of symptoms of uterine fibroids has not been accepted by the PBAC.

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

3 Background

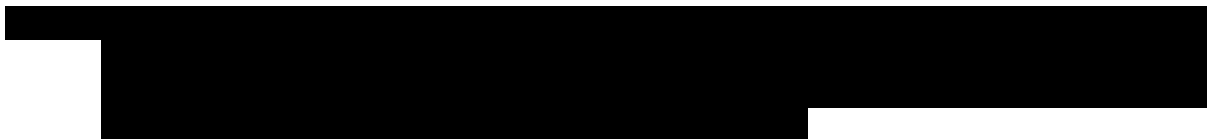
- 3.1 Ulipristal was approved for registration by the TGA for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age at the 309th meeting of the Advisory Committee on Prescription Medicines on 1 April 2016.
- 3.2 This was the first submission of ulipristal to the PBAC for the treatment of moderate-severe symptoms of uterine fibroids.

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

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 submission proposed ulipristal as an alternative medical management option to GnRH analogues with or without hormonal add-back therapy. The recommended dose regimen for ulipristal is one tablet of 5 mg taken orally once daily for treatment courses of up to three months each. Treatments should only be initiated when menstruation has occurred:
- The first treatment course should start during the first week of menstruation;
 - Re-treatment courses should start, at the earliest, during the first week of the second menstruation following the previous treatment course completion.
- 4.3 The submission stated that ulipristal could be used in a broad range of clinical scenarios, including:
- 1) Short-term use (three months) in patients indicated for and planning surgery, as a means of stabilising symptoms, and potentially facilitating less invasive surgical techniques;
 - 2) Medium-term use, as temporary symptom relief, in older patients approaching menopause, after which the condition generally resolves without further intervention;
 - 3) Medium-term use, to provide symptom relief and improve fertility outcomes, in patients planning pregnancy;
 - 4) Longer-term intermittent therapy, of potentially several years' duration, as a preferred alternative to currently available medical and/or surgical management options.

The proposed treatment algorithm, presented in the submission, did not differentiate between these four clinical scenarios.



- 4.4 The ESC noted that the treatment algorithm was updated in the Pre-Sub-Committee Response (PSCR). However, more clarification was still required in terms of the definition of moderate to severe symptoms of uterine fibroids and the treatment of these in the Australian context, particularly with respect to the management of patients presenting with abnormal uterine bleeding only, and those patients who are not eligible for or have a preference against surgical options. The ESC recommended that further clinical advice be sought from The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) regarding current clinical practice.
- 4.5 RANZCOG were supportive of a short-term three-month course of ulipristal as an oral alternative to GnRH analogues to reduce the size of fibroids prior to surgery. RANZCOG also noted that although repeated three-month courses may have a role in the long-term management of fibroids, more data was required to address concerns regarding endometrial thickness, the long-term benefits of one or two courses of ulipristal and the long-term side effect profile and efficacy of ulipristal.
- 4.6 The sponsor requested to remove the medium and long-term (intermittent) use of ulipristal from the proposed restriction in the Pre-PBAC response as the issues surrounding this clinical scenario including treatment algorithm, definition and size of target population, identification of the appropriate main comparator, evidence of long-term effectiveness and safety, and approach to the economic evaluation could not be adequately addressed in the Pre-PBAC response. Therefore, the sponsor focused the response on addressing the issues relating to the use of ulipristal in the short-term, pre-surgical setting. The PBAC considered all of the original four requested treatment scenarios in its deliberations, taking note of the Pre-PBAC request above.

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

5 Comparator

- 5.1 The submission nominated goserelin, either alone or in conjunction with hormonal add-back therapy with tibolone, as the main comparator. The submission indicated that ulipristal would substitute for:
- Goserelin in the case of short-term or pre-surgical use (Clinical scenario 1 above), and
 - Goserelin in conjunction with hormonal add-back therapy (ongoing use), for medium to long-term use (Clinical scenarios 2-4 above).
- 5.2 Goserelin is currently listed on the PBS for the treatment of carcinoma of the prostate, endometriosis and breast cancer; it is not listed on the PBS for the treatment of uterine fibroids.
- 5.3 The sponsor stated in the PSCR that PBS and private goserelin prescribing occurs for uterine fibroids in practice. The ESC noted that supportive evidence for this claim

was not provided. The PBAC noted that this was not addressed in the Pre-PBAC response.

- 5.4 For the short-term use of ulipristal in patients planning surgery, goserelin is an appropriate comparator, as the TGA indication for goserelin includes its use in the management of uterine fibroids as an adjunct to surgery to facilitate the operative technique and reduce operative blood loss. As the aims of pre-operative use of goserelin include facilitating the operative technique and reducing operative blood loss, the relevant comparison would be ulipristal followed by surgery versus goserelin followed by surgery. Surgery with no pre-treatment may also be an appropriate comparator in this setting. The sponsor agreed with this suggestion in the PSCR however, no surgical outcome data were provided to enable this comparison.
- 5.5 The evaluation and the ESC noted that continuous medium-long term use of goserelin, with or without add-back therapy, was not considered an appropriate comparator for repeated intermittent use of ulipristal. The Product Information (PI) for goserelin states that, in the treatment of uterine fibroids, goserelin may be used for a period of 3 to 6 months. This is consistent with recommendations in current evidence-based clinical management guidelines*. The PSCR cited several examples from previous PBAC considerations of other medicines that were accepted as comparators despite not being PBS listed and/or TGA registered for the indication in question. While the ESC noted these examples, detailed clinical evidence to support the claimed use of goserelin outside of the TGA registration or PBS listing in Australian clinical practice was not provided by the sponsor. The ESC further noted that the claim of goserelin use with or without tibolone for medium to long-term treatment of uterine fibroids was not supported by sufficient clinical evidence. For medium to long-term use of ulipristal, it was suggested that surgery (with or without prior short-term goserelin therapy) and other interventions (including uterine artery embolisation) may be more appropriate comparators. Given the sponsor requested removal of medium and long-term use of ulipristal from the submission, the PBAC did not nominate comparators for the medium to long-term use of ulipristal, however they did consider that goserelin was not an appropriate comparator in these scenarios.

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.

* National Institute for Health and Care Excellence. NICE Pathways: Treatment options for heavy menstrual bleeding 2015 [updated 27 July 2015; cited 18 March]. Available from: <https://pathways.nice.org.uk/pathways/heavy-menstrual-bleeding>. Vilos GA, Allaire C, *et al.* SOGC Clinical Practice Guideline: The management of uterine leiomyomas. *J Obstet Gynaecol Can.* 2015; 37 (2):157-81

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ulipristal including fewer side effects compared to GnRH analogues, avoidance of surgery and significant improvements with menstrual symptoms. As stated in paragraph 4.6 above, RANZCOG provided clinical input regarding the likely use of and effectiveness of ulipristal in moderate to severe uterine fibroids.

Clinical trials

6.3 The submission did not provide either a direct or an indirect comparison of ulipristal versus the nominated comparator. The submission was based on two separate sets of studies of ulipristal and goserelin and stated that, given the significant heterogeneity in the design, comparator(s), patient population, duration of treatment and follow-up, outcomes evaluated, analysis and reporting protocols and general quality of the studies, no formal meta-analysis or indirect treatment comparison was attempted. Given the exchangeability and transitivity issues between the two evidence sets, this is reasonable.

6.4 Details of the studies presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ulipristal randomised trials		
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, Tatarchuk 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.
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.
PEARL III (PGL09-026)	A phase III, multicentre, clinical study investigating the efficacy and safety of 3-months open-label treatment with PGL4001, followed by a randomised, double-blind placebo controlled period of 10 days treatment with progestin, in subjects with myomas and heavy uterine bleeding.	June 2012

Espejo 1999	Espejo MR, Espejo AI, <i>et al.</i> Add-back therapy of uterine fibroids with tibolone and goserelin.	<i>European Journal of Obstetrics & Gynecology and Reproductive Biology</i> 1999; 86 (Suppl 1);S19.
Parazzini 1999	Parazzini F, Bortolotti A, <i>et al.</i> Goserelin acetate to avoid hysterectomy in pre-menopausal women with fibroids requiring surgery.	<i>European Journal of Obstetrics & Gynecology and Reproductive Biology</i> 1999; 87:31-33.
Lim 2008	Lim SS, Sockalingam JK and Tan PC. Goserelin versus leuprolide before hysterectomy for uterine fibroids.	<i>International Journal of Gynecology and Obstetrics</i> 2008; 101:178-183.
<i>Systematic reviews</i>		
Moroni 2015	Moroni RM, Martins WP, <i>et al.</i> Add-back therapy with GnRH analogues for uterine fibroids.	<i>Cochrane Database of Systematic Reviews</i> 2015; Issue 3. Art No.: CD010854. DOI: 10.1002/14651858.CD010854.pub2.
Lethaby 2001	Lethaby A, Vollenhoven B and Sowter MC. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids.	<i>Cochrane Database of Systematic Reviews</i> 2001; Issue 2. Art. No.: CD000547. DOI:10.1002/14651858.CD000547.

Source: Table B-3, p26 of the submission.

- 6.5 The submission did not justify the inclusion or exclusion of the goserelin studies. It is not clear why some studies of limited relevance were included, while others were excluded. The PSCR stated that the goserelin studies were not excluded but were considered adequately summarised in the included systematic reviews. The ESC noted that uncertainty regarding the selection of studies for inclusion in the submission remained.
- 6.6 The submission included an abstract of Espejo 1999 (Table 1) for the short-term use of goserelin. Given the lack of information available for this study, and as it did not include a comparison of goserelin with a relevant comparator (all patients received goserelin), this study was not included in the evaluation.
- 6.7 The submission also presented evidence for the medium-long term use of goserelin ± add-back therapy (Parazzini 1999 and Caird 1997, Table 1). Since the PI for goserelin does not recommend its use beyond six months in the treatment of symptoms of uterine fibroids, and given the lack of relevant outcomes reported and the high risk of bias, the results of these studies were only evaluated as supplementary evidence.
- 6.8 The key features of the comparative and non-comparative studies of ulipristal and of goserelin are summarised in the table below. The evidence was presented firstly, for the short-term use of ulipristal (relevant to clinical scenario 1) and, secondly, for the repeated intermittent medium-long term use of ulipristal (relevant to clinical scenarios 2-4).

Table 2: Key features of the included evidence

Trial	Design/ duration	Risk of bias	Patient population	Outcomes
Ulipristal – short-term use (Clinical scenario 1)				
PEARL I	RCT comparing UPA 5 mg (n=96) and UPA 10 mg (n=98) with placebo (n=48), 3 months	Low	Pre-menopausal women with moderate to severe symptoms of uterine fibroid	1) Percentage of patients with reduction of uterine bleeding at Week 13, defined as a PBA chart score of less than 75 2) Change in total fibroid volume from screening to Week 13, assessed by MRI 3) Reduction in uterine volume from screening to Week 13, assessed by MRI 4) Changes in haemoglobin, haematocrit, and ferritin levels
PEARL II	Non-inferiority RCT comparing UPA 5 mg (n=102) and UPA 10 mg (n=103) with leuprorelin (n=102), 3 months	Low	As above	1) Proportion of patients with reduction of uterine bleeding at Week 13, defined as above 2) Change in uterine volume from baseline to Week 13 3) Change in volume of the 3 largest fibroids from baseline to Week 13 4) Change in haemoglobin, haematocrit and ferritin levels
Ulipristal – medium to long-term use (Clinical scenarios 2-4)				
PEARL III and extensions	RCT (N=201) and Extension 1 (N=132) all patients received UPA 10 mg (one 3-month course in the initial trial, three courses in Extension 1). Patients were randomised to receive either progestin or placebo for 10 days after each UPA treatment course.* Patients received additional four courses of open-label treatment with UPA 10 mg in Extension 2 (n=64)	Unclear**	As above	1) Subjects in amenorrhoea at the end of each treatment course; 2) Change in volume of 3 largest fibroids
PEARL IV	RCT comparing UPA 5 mg (n=228) with UPA 10 mg (n=223) (four 12-week treatment courses)	Unclear**	As above	1) Percentage of subjects in amenorrhoea at the end of both treatment courses 1 and 2; 2) Percentage of subjects in amenorrhoea at the end of all four treatment courses. 3) Controlled bleeding in the last 56 days of each individual treatment course 4) Change in volume of the 3 largest fibroids 5) Change in uterine volume
Goserelin – short-term use (≤ 6 months) (Clinical scenario 1)				
Lim 2008	RCT comparing goserelin (n=34)	High	As above	1) Preoperative haemoglobin

Trial	Design/ duration	Risk of bias	Patient population	Outcomes
	with leuprorelin (n=32) for 3 months			level 2) Operative time 3) Intraoperative blood loss 4) Reduction in uterine size 5) Blood transfusion 6) Intraoperative complications
Morris 2008	RCT comparing goserelin + placebo for 6 months (n=25), goserelin + tibolone for 6 months (n=25) and goserelin + placebo for 3 months followed by goserelin + tibolone for 3 months (n=25).	High	As above	Changes in uterine and fibroid volume as secondary outcomes
Lethaby 2001	Systematic review of RCTs comparing GnRH analogue to either placebo, no treatment, or other medical therapy prior to surgery	Unclear	Unclear	1) Reduction in uterine volume and/or fibroid volume 2) Change in haematologic indices 3) Duration of operation 4) Intra-operative blood loss 5) Frequency of blood transfusions 6) Post-operative morbidity

GnRH = gonadotrophin-releasing hormone; MRI = magnetic resonance imaging; PBA = pictorial blood-loss assessment; RCT = randomised controlled trial; UPA = ulipristal acetate

* In PEARL III, 98 patients were randomised to progestin and 103 to placebo. In PEARL III Extension 1, 64 patients received progestin and 68 received placebo.

** PEARL III and IV were non-comparative in respect to ulipristal (all patients received ulipristal). There was potential for bias in attributing causation and assessment of the severity of adverse events.

Leuprorelin – a GnRH agonist listed on the PBS for prostate cancer, not TGA registered for treatment of fibroids. The submission referred to as leuprolide acetate. In Australia, this is referred to as leuprorelin acetate (both TGA and PBS).

Source: compiled during the evaluation.

- 6.9 As the dose of ulipristal used in PEARL III (10 mg daily) is not consistent with the recommended dose in the draft PI (5 mg daily), this trial was evaluated as supplementary evidence.
- 6.10 Lethaby 2001 was a Cochrane systematic review of randomised controlled trials (RCTs) comparing GnRH analogue treatment versus placebo, no treatment, or other medical therapy prior to surgery for uterine fibroids. The submission did not provide details of the seven individual goserelin trials included in the review. The risk of bias in these studies could not be fully assessed based on the data provided in Lethaby 2001. The references for these studies were provided with the PSCR. The ESC considered that these studies did not substantially add to the evidence base for goserelin.
- 6.11 Overall, the evidence presented in the submission for the short-term effectiveness of goserelin consisted of relatively small, predominantly open-label trials, with insufficient details to assess the risk of bias.

Comparative effectiveness**Short-term use of ulipristal in patients planning surgery (Clinical scenario 1)**

6.12 The main results of the short-term ulipristal trials PEARL I and PEARL II are presented below.

Table 3: Main results in the short-term ulipristal trials PEARL I and PEARL II

PEARL I	Ulipristal 5 mg	Placebo	Absolute difference (95% CI)	Relative risk (95% CI)
<i>PBA chart score < 75 at Week 13, n/N (%), ITT analysis</i>				
n/N (%) ^a	86/94 (91.5%)	9/48 (18.8%)	72.7% (55.1%, 83.2%)	4.88 (2.70, 8.82)
<i>% change in total fibroid volume from screening to Week 13 (cm³)^b</i>				
Median (range)	-21.2% (-41.2 to -1.1)	3.0% (-19.7 to 23.0)	-22.6% (-36.1%, -8.2%)	
<i>% change in uterine volume from screening to Week 13 (cm³)</i>				
Mean (SD)	-8.67% (34.4)	5.91% (20.1)		
<i>Log₁₀ volume, mean change (SE)</i>				
Mean (SE)	-0.072 (0.015)	0.007 (0.019)	-0.079 (-0.131, -0.028)	
PEARL II	Ulipristal 5 mg	Leuprorelin	Absolute difference (95% CI)	Relative risk (95% CI)
<i>PBA chart score < 75 at Week 13^a, n/N (%)</i>				
PP analysis	84/93 (90.3%)	82/92 (89.1%)	1.2% (-9.3%, 11.8%) ^c	1.01 (0.92, 1.12)
ITT analysis	90/98 (91.8%)	87/98 (88.8%)	3.1% (-6.9%, NR)	
<i>% change in total volume of 3 largest fibroids from screening to Week 13 (cm³)</i>				
Median (range)	-35.6% (-98.0 to 230.8)	-53.5% (-91.0 to 527.7)		
<i>Log₁₀ volume, mean change (SE)</i>				
PP analysis	-0.179 (0.037)	-0.268 (0.037)	0.089 (-0.003, 0.181)	
ITT analysis	-0.179 (0.036)	-0.215 (0.036)	0.095 (0.005, 0.186)	
<i>% change in uterine volume from screening to Week 13 (cm³)</i>				
Mean (SD)	-1.3% (123.8)	-39.0% (38.6)		
<i>Log₁₀ volume, mean change (SE)</i>				
PP analysis	-0.077 (0.029)	-0.246 (0.028)	0.169 (0.097, 0.241)	
ITT analysis	-0.079 (0.028)	-0.240 (0.028)	0.161 (0.091, 0.232)	

PBA = pictorial blood-loss assessment; CI = confidence interval; NR = not reported; SD = standard deviation; SE = standard error; PP = per protocol; ITT = intention to treat; LOCF = last observation carried forward.

^a Last observation carried forward

^b Change in total fibroid volume, defined as the sum of all the individual fibroid volumes

^c Pre-specified non-inferiority margin -20%

Figures in bold indicate a statistically significant result.

Note: The PBA chart scale ranges from 0 to >500 (with no defined upper limit), with higher scores indicating a greater severity of bleeding. A PBA chart score > 100 indicates menorrhagia.

Source: Tables B-26, B-27 and B-32, pp58-61 of the submission; Tables B-41, B-44 and B-45, pp69-71 of the submission; Table 21, p107 PEARL I CSR; Tables 14.2.2.2, 14.2.11.2, and 14.2.13.2 PEARL II CSR; Table 2, Donnez *et al.* 2012a[†]; Table 2 Donnez *et al.* (2012b).[‡]

[†] Donnez J, Tatarчук TF, *et al.* Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med.* 2012; 366 (5):409-20.

[‡] Donnez J, Tomaszewski J, *et al.* Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med.* 2012; 366 (5):421-32.

- 6.13 The results of PEARL I supported the claim that a single 3-month course of ulipristal is superior to placebo in terms of controlling abnormal uterine bleeding and reducing both fibroid and uterine volume in pre-menopausal women who are eligible for surgical management. Ulipristal was also superior to placebo in increasing haemoglobin levels in anaemic patients who were also receiving oral iron supplementation.
- 6.14 The results of PEARL II supported the claim that a single three-month course of ulipristal 5 mg daily is non-inferior to three months of leuprorelin therapy in controlling abnormal uterine bleeding, based on a pre-specified non-inferiority margin of -20% in the proportion of patients with Pictorial Bleeding Assessment (PBA) chart score[§] <75 at Week 13, but leuprorelin may be more effective in reducing both fibroid and uterine volume.
- 6.15 Neither of the two short-term ulipristal trials evaluated possible treatment-related differences in surgical outcomes, including the potential to allow less invasive surgical procedures.
- 6.16 The results for the comparison of goserelin and leuprorelin, when used short-term prior to hysterectomy (Lim 2008), are presented below.

Table 4: Outcomes for short-term (3 months) use of goserelin versus leuprorelin (Lim 2008)

Lim 2008	Goserelin N=34	Leuprorelin N=31	p-value ^a
Haemoglobin, g/dL, mean (SD)			
Baseline	9.9 (1.7)	10.1 (1.4)	0.89
Admission for surgery	11.9 (1.4)	12.0 (1.5)	
Uterine volume (mL), mean (SD)			
Baseline	597 (247)	578 (211)	0.94
Admission for surgery	438 (237)	433 (188)	
% decrease in mean volume	26.6%	25.1%	

SD = standard deviation

^a Goserelin versus leuprorelin

Figures in italics were calculated during the evaluation.

Source: Table (unnumbered), p46 and Tables B-90 and B-91, pp123-4 of the submission.

- 6.17 Lim 2008 demonstrated that goserelin and leuprorelin appear to have reasonably similar effectiveness in terms of improving haemoglobin levels and reducing uterine volume, when administered for three months. In addition to exchangeability or transitivity concerns, the outcomes in Lim 2008 were reported in a manner that did not allow an indirect comparison of ulipristal and goserelin to be performed, i.e. using leuprorelin as the common comparator.
- 6.18 Based on the evidence presented in the systematic review by Lethaby 2001, goserelin was superior to both no pre-treatment and placebo in reducing uterine and fibroid size, and in improving haematologic indices prior to surgery. As all outcomes were reported as mean pre-operative values, rather than the change from baseline, and as baseline values were not provided, an indirect comparison of ulipristal and goserelin, with placebo as the common comparator, was not feasible.

[§] The PBA chart scale ranges from 0 to >500 (with no defined upper limit), with higher scores indicating a greater severity of bleeding. A PBA chart score > 100 indicates menorrhagia.

- 6.19 Given the absence of direct evidence, and the lack of comparable outcomes between the ulipristal and goserelin trials, it was not possible to draw any conclusions regarding the relative effectiveness of short-term ulipristal and goserelin in terms of either reduction of abnormal uterine bleeding, reduction in uterine and/or fibroid volume, or surgical outcomes. The ESC and PBAC agreed with this conclusion.

Repeated intermittent medium-long term use of ulipristal (Clinical scenarios 2-4)

- 6.20 The results of PEARL IV indicated that four intermittent courses of ulipristal 5 mg/daily were effective in controlling abnormal uterine bleeding and reducing fibroid and uterine volumes. However, given the non-comparative nature of PEARL IV, the magnitude of the treatment effect is unclear. The effectiveness of repeated intermittent courses of ulipristal in either delaying or preventing the requirement for surgery or other interventions such as uterine artery embolisation (UAE) was not evaluated.
- 6.21 The PBAC noted that the submission did not present any evidence on the long-term effectiveness of ulipristal 5 mg daily beyond four intermittent three-month courses.

Comparative harms

Short-term use of ulipristal in patients planning surgery (Clinical scenario 1)

- 6.22 The key adverse events (AEs) in PEARL I are summarised below. 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 (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%)
TEAEs occurring in at least 3% of the patients in any group ^a			
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

Figures in italics were calculated during the evaluation.

Source: Tables B-38 and B-39, pp66-67 of the submission; Table 3, p418 Donnez *et al* (2012a)**

- 6.23 Table 6 presents the results for the primary safety endpoints in PEARL II, for ulipristal compared to the GnRH analogue leuprorelin.

Table 6: Primary safety outcomes in PEARL II (ulipristal versus leuprorelin)

	Ulipristal 5 mg (N=97)	Leuprorelin (N=101)	Absolute difference (95% CI)
Log ₁₀ oestradiol level at Week 13 (pg/mL), mean (SE)	1.897 (0.041)	1.381 (0.041)	0.516 (0.413, 0.619)
Hot flush, n (%)	23 (23.7%)	63 (62.4%)	-28.3% (-40.6%, -14.6%)

CI = confidence interval; SE = standard error

Figures in bold indicate statistically significant results.

Source: Tables B-50 and B-51, p76 of the submission

- 6.24 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.

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

6.25 The key AEs occurring in PEARL II are summarised below.

Table 7: Summary of key adverse events in the PEARL II (ulipristal versus leuprorelin)

PEARL II	Ulipristal 5 mg n (%) N=97	Leuprorelin n (%) N=101	Absolute difference (95% CI)
At least 1 AE	76 (78.4%)	90 (89.1%)	-10.8% (-21.0%, -0.6%)
At least 1 TEAE	75 (77.3%)	85 (84.2%)	-6.8% (-17.8%, 4.1%)
Drug-related TEAE	57 (58.8%)	71 (70.3%)	-11.5% (-24.8%, 1.7%)
At least 1 Serious TEAE	5 (5.2%)	4 (4.0%)	1.2% (-4.6%, 7.0%)
TEAE leading to discontinuation	1 (1.0%)	6 (5.9%)	-4.9% (-9.9%, 0.1%)
TEAE leading to study withdrawal	1 (1.0%)	5 (5.0)	-3.9% (-8.6%, 0.8%)
Serious TEAE in follow-up (Week 17-38)	3 (3.1%)	2 (2.0%)	1.1% (-3.3%, 5.5%)
AEs occurring in at least 5% of the patients in any group ^a			
Hot flush	25 (25.8%)	66 (65.3%)	-39.6% (-52.3%, -26.8%)
Headache	25 (25.8%)	29 (28.7%)	-2.9% (-15.3%, 9.5%)
Procedural pain	9 (9.3%)	9 (8.9%)	0.4% (-7.6%, 8.4%)
Abdominal pain	6 (6.2%)	14 (13.9%)	-7.7% (-15.9%, 0.6%)
Nausea	6 (6.2%)	6 (5.9%)	0.2% (-6.4%, 6.9%)
Nasopharyngitis	6 (6.2%)	2 (2.0%)	4.2% (-1.3%, 9.7%)
Anaemia	5 (5.2%)	5 (5.0%)	0.2% (-5.9%, 6.3%)
Breast pain or tenderness	5 (5.2%)	2 (2.0%)	3.2% (-2.0%, 8.3%)
Pharyngitis	5 (5.2%)	2 (2.0%)	3.2% (-2.0%, 8.3%)
Fatigue	4 (4.1%)	3 (3.0%)	1.1% (-4.0%, 6.3%)
Influenza	2 (2.1%)	5 (5.2%)	-2.9% (-8.0%, 2.2%)
Insomnia	2 (2.1%)	5 (5.2%)	-2.9% (-8.0%, 2.2%)
Acne	0	5 (5.0%)	-5.0% (-9.2%, 0.7%)

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

Figures in italics were calculated during the evaluation.

Source: Tables B-52 and B-53, pp77-78 of the submission; Table 3, p430 Donnez *et al* (2012b)^{††}

6.26 Overall, ulipristal 5 mg appeared to have a more favourable AE profile compared to leuprorelin. In Lim 2008, the incidence of hot flushes was similar in the goserelin and the leuprorelin treatment arms (52.9% and 61.3%, respectively).

6.27 In general, the incidence of AEs in the ulipristal 5 mg arm of PEARL II appeared to be higher than in the ulipristal 5 mg arm of PEARL I (e.g. hot flushes were reported in 2.1% of patients in PEARL I compared to 25.8% in PEARL II). The reason for this difference was not clear. Across the two trials, the most common AEs in the ulipristal arms were headaches and hot flushes, most of which were mild to moderate.

Repeated intermittent medium-long term use of ulipristal (Clinical scenarios 2-4)

6.28 No evidence was provided for the safety of long-term use of ulipristal 5 mg/daily; adequate data were only available for up to four repeated treatment courses. All safety data was non-comparative. The incidence of TEAEs was highest during the first treatment course; the majority were of mild to moderate intensity.

6.29 The second PEARL III extension study (PGL11-024) provided safety data for 64 patients from the first PEARL III extension, who received a further four 3-month

^{††} Donnez J, Tomaszewski J, *et al*. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med*. 2012; 366 (5):421-32.

courses of ulipristal 10 mg (total of 8 intermittent courses). While this study did not raise any additional safety issues, the study was too small to reliably identify less common treatment-related AEs.

- 6.30 There are insufficient long-term safety data to determine if ulipristal increases the risk of endometrial abnormalities, including possible malignant changes. The safety for a human embryo/foetus is unknown.
- 6.31 The sponsor has stated in the PSCR that there are ongoing long-term safety studies in the EU that may provide further information in regards to the long-term safety of ulipristal that may be available in the future.

Clinical claim

- 6.32 The submission described ulipristal as “qualitatively” non-inferior in terms of comparative effectiveness and “qualitatively” superior in terms of comparative safety over goserelin (with or without tibolone). As acknowledged in the submission, there was insufficient comparative evidence to provide a “quantitative” estimate of the comparative effectiveness and safety of ulipristal and goserelin, in either the short-term or the medium-long term.

Short-term use of ulipristal before surgery (Clinical scenario 1):

- 6.33 There was insufficient evidence to make any conclusions regarding the comparative effectiveness and safety of the short-term use of ulipristal and goserelin prior to surgery.

The evidence presented in the submission supported the following conclusions:

- In comparison to placebo (or no treatment):
 - A single 13-week course of ulipristal was superior to placebo in terms of controlling abnormal uterine bleeding and reducing both fibroid and uterine volume in pre-menopausal women who are eligible for surgery;
 - Goserelin is superior to both no pre-treatment and placebo in reducing both uterine and fibroid size, and in improving haematologic indices prior to surgery;
 - Given the considerable heterogeneity between the goserelin trials, the likely magnitude of these benefits in the proposed PBS population is highly uncertain;
- Compared to the alternative GnRH analogue leuprorelin:
 - A single three-month course of ulipristal was non-inferior to three months of leuprorelin in controlling abnormal uterine bleeding;
 - Leuprorelin may be more effective than ulipristal in reducing both fibroid and uterine volume;
- 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;
- In terms of safety:
 - Compared to leuprorelin, ulipristal was associated with a less profound suppression of oestradiol levels and a lower incidence of hot flushes; and

- Overall, ulipristal 5 mg appeared to have a more favourable AE profile compared to leuprorelin.

Repeated intermittent medium-long term use of ulipristal (Clinical scenarios 2-4):

6.34 Given the lack of evidence for the medium-long term use of goserelin, it was not possible to make any conclusions regarding the comparative effectiveness and safety of ulipristal and goserelin (with or without add-back therapy) in these clinical scenarios.

The evidence presented in the submission supported the following conclusions:

- The effectiveness of three-month courses of ulipristal 5 mg, in terms of controlling abnormal uterine bleeding and reducing fibroid volume, was maintained over four intermittent courses;
- In the absence of comparative long-term data, it was not possible to determine the extent to which repeated intermittent courses of ulipristal may prevent or delay the requirement for surgery or other interventions such as UAE;
- There were no safety data for the long-term effects of prolonged treatment with ulipristal on the endometrium (including possible malignant changes).

6.35 Advice received from RANZCOG similarly noted (see paragraph 4.6) that ulipristal may cause specific endometrial changes and/or endometrial hyperplasia but that these do not appear to be pre-malignant in the short-term. RANZCOG noted there were no other serious adverse effects reported with short-term use. RANZCOG also stated that long-term data were currently not available but would be required, given that repeated courses over many years may be needed in some woman. Specific organs/tissues requiring long-term study include the endometrium and breast.

6.36 In relation to the claims for specific uses, as listed for each clinical scenario in the submission:

- There was no evidence available to demonstrate that ulipristal was effective in facilitating less invasive surgical techniques in patients planning surgery (Clinical scenario 1);
- For patients approaching menopause, there was no evidence available to demonstrate the effectiveness of medium term use of ulipristal in terms of preventing the requirement for surgery (or other interventional management such as UAE) prior to reaching menopause (Clinical scenario 2);
- There was no evidence available to demonstrate that ulipristal improves fertility outcomes in patients planning pregnancy (Clinical scenario 3); and
- There was no evidence available to demonstrate that ulipristal prevents the requirement for surgical management or other interventions such as UAE (Clinical scenario 4).

6.37 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data with a lack of direct and indirect evidence to allow for a comparison. The PBAC noted that no data was presented to assess the impact of treatment with ulipristal on surgical outcomes.

- 6.38 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data with no direct or indirect comparison possible.

Economic analysis

- 6.39 The submission presented two alternative cost-minimisation analyses:
- i) Ulipristal 5 mg daily for 12 weeks versus goserelin 3.6 mg every 28 days for three treatments, as short-term treatment for patients with moderate to severe symptoms of uterine fibroids, typically prior to surgery; and
 - ii) Repeated intermittent courses of ulipristal 5 mg for 12 weeks, each separated by a drug free interval of approximately 6 weeks, versus chronic therapy with goserelin 3.6 mg every 28 days + tibolone 2.5 mg daily, as longer term medical management for patients with moderate to severe symptoms of uterine fibroids. The submission used an arbitrary time-frame of one year for this analysis.
- 6.40 The equi-effective doses were estimated from the respective PIs for each drug. As noted above, the equivalent efficacy of ulipristal and goserelin was not substantiated by the evidence provided in the submission. In addition, the dosage and administration recommendations in the goserelin PI state that, in the treatment of uterine fibroids, goserelin may only be used for a period of three to six months.
- 6.41 The PBAC agreed with the evaluation that a cost-minimisation approach of ulipristal versus goserelin was not considered appropriate given that goserelin 3.6 mg is not listed on the PBS for this indication. Therefore, goserelin at the PBS price listed for other indications (carcinoma of the prostate, endometriosis and breast cancer) may not be cost-effective for the treatment of moderate-severe symptoms of uterine fibroids in the Australian clinical setting.

Drug cost/patient/course

- 6.42 Single 12-week course: \$██████ per patient.
This was based on a dispensed price for maximum quantity (DPMQ) of \$██████ for 28 tablets (4 weeks supply). The nominated comparator is not PBS-listed for this indication.
- 6.43 Long-term repeated intermittent 12-week courses: \$██████/patient/year
This was based on the assumption that each 12-week course of ulipristal is separated by a drug-free interval of 42 days (total cycle length of 126 days, 2.9 cycles per year). No justification was provided for this assumption.

Estimated PBS usage & financial implications

- 6.44 This submission was considered by the Drug Utilisation Sub-committee (DUSC).
- The financial implications are based on a DPMQ for ulipristal of \$██████, as presented in the Excel Section E Workbook provided in the submission.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Cost of ulipristal					
<i>i) Short-term treatment (12-week course)</i>					
Number treated					
Scripts per year ^a					
Estimated net cost to PBS/RPBS (short-term patients)					
<i>Net cost to PBS/RPBS</i>	\$	\$	\$	\$	\$
<i>ii) Long-term treatment (repeated intermittent courses)</i>					
Number treated					
Scripts per year ^a					
Estimated net cost to PBS/RPBS (long-term patients)					
<i>Net cost to PBS/RPBS</i>	\$	\$	\$	\$	\$
Estimated total net cost for ulipristal					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Cost-offsets					
Goserelin	\$	\$	\$	\$	\$
Other drugs ^b	\$	\$	\$	\$	\$
<i>Corrected^c</i>	\$	\$	\$	\$	\$
Estimated total cost offsets	\$	\$	\$	\$	\$
<i>Corrected^c</i>	\$	\$	\$	\$	\$
Estimated total net cost to the PBS/RPBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
<i>Corrected^d</i>	\$	\$	\$	\$	\$

^a Assuming [redacted] scripts per patient for short-term treatment and [redacted] scripts per patient per year for long-term treatment, as estimated by the submission.

^b Includes combination oral contraceptives, tranexamic acid and levonorgestrel intrauterine system

^c The submission failed to include the cost offsets to the PBS and RPBS for levonorgestrel intrauterine system

^d Not including cost-offsets for goserelin but including cost-offsets for levonorgestrel intrauterine system

Figures in italics calculated during the evaluation

Source: Tables E-2, E-3 and E-4, pp147-149 of the submission and Section E Workbook.xlsx attached to the submission.

The redacted table shows that at year 5, the number of patients treated per year with ulipristal would be less than 10,000 for short-term treatment and 10,000 – 50,000 for long-term treatment. The net cost to the PBS/RPBS, allowing for cost-offsets for Goserelin and other drugs, would be less than \$10 million (uncorrected price) or \$30 - \$60 million in year 5 (corrected for cost-offsets for levonorgestrel intrauterine system).

6.45 The number of patients likely to be treated was highly uncertain and the DUSC agreed that the population was highly likely to be underestimated:

- There was limited evidence available for the prevalence of clinically relevant fibroids causing moderate to severe symptoms in patients of reproductive age;
 - The applicability of the prevalence of diagnosed uterine fibroid reported in Zimmermann et al (2012) of 7% to the Australian population was uncertain;
 - The DUSC considered the estimate of 14.4% of patients having moderate to severe symptoms of uterine fibroids based on the proportion of patients in Zimmermann et al who experienced chronic pelvic pain on all or most days of the month (and clinical advice) to be an underestimate. The DUSC considered that chronic pelvic pain was more likely a severe symptom indicator and that moderate to severe symptoms would likely include other severity indicators reported in Zimmermann et al, such as prolonged

duration of menstrual bleeding (37.3%) and pressure on the bladder or inside the abdomen (32.6%).

- The relative proportions of patients assumed to receive surgery, short-term medical therapy and medium-long term medical therapy, in both the scenario without ulipristal and the scenario in which ulipristal is listed on the PBS, was based on informal clinical opinion. The DUSC considered that the overall proportion of patients estimated to receive ulipristal were underestimated and that the removal of ■% of patients from the eligible population for immediate surgery (without medical pre-treatment) may have contributed to the underestimation. The DUSC considered that the availability of a tablet may change the decision context for a patient and may result in a higher proportion of patients receiving medical pre-treatment and delaying surgery.
 - The DUSC considered that for the short-term pre-surgery population, where use of ulipristal would essentially be a once in a lifetime treatment, an incidence approach accounting for a prevalent pool in the first year may be more appropriate. The DUSC recognised that this approach may be limited by data, but that triangulation with available data on surgical interventions may reduce the uncertainty of the estimates. The sponsor and the PBAC agreed with this approach. Therefore, the PBAC recommended that any revised estimates should use an incidence approach and be subject to a Risk Share Arrangement.
 - The DUSC considered that given there are currently no PBS-listed drugs for the treatment of moderate to severe symptoms of uterine fibroids:
 - The assumption that listing of ulipristal would not increase the proportion of patients receiving both short-term and medium-long term medical therapy was not adequately justified; and
 - The uptake of ulipristal, especially in the short-term pre-surgical setting, was likely to be underestimated.
- 6.46 The submission inappropriately deducted cost savings resulting from the substitution of ulipristal for goserelin. Goserelin is not listed on the PBS for this indication. The DUSC indicated that the submission did not provide any evidence that PBS subsidised goserelin is currently prescribed outside of the restriction for uterine fibroids. The DUSC also considered that it is unlikely that patients would receive 13.04 goserelin implants per year as used in the submission's long-term treatment utilisation assumptions as the TGA registration for goserelin for uterine fibroids indicates treatment for only three to six months as an adjunct to surgery, to facilitate the operative technique and reduce operative blood loss. Additionally, treatment with goserelin may result in substantial adverse effects including reduced bone density that also makes likely long-term use outside registration less likely.
- 6.47 Despite previously stating that pharmacological therapies, other than goserelin, are generally reserved for patients with milder symptoms and/or for short-term symptom alleviation, the submission offset costs associated with substitution for these drugs, in both the short-term treatment and the medium-long term treatment settings.
- 6.48 Due to the inappropriate deduction of potential savings resulting from substitution for goserelin, there is potential for the net cost/year for the PBS/RPBS to be considerably greater than estimated in the submission. The DUSC noted that removing the cost-offsets for goserelin from the estimates could change the net cost

to the PBS/RPBS in Year 5 from less than \$10 million to \$30 - \$60 million, which is considerably higher than estimated in the submission. The PBAC considered that the PBS financial estimates should exclude cost offsets for goserelin.

- 6.49 The DUSC considered that the uterine fibroid related symptoms of patients presenting for treatment would be of a moderate to severe nature, resulting in a low likelihood of use beyond the requested restriction for milder symptoms.

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

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend that ulipristal be listed on the PBS for the treatment of moderate to severe uterine fibroids on the basis that the clinical place in therapy was not adequately established, the nominated comparator, goserelin, is not PBS listed for the treatment of uterine fibroids and its use in clinical practice was not substantiated, the comparative effectiveness and safety of ulipristal compared to goserelin was not established, and no evidence was presented assessing the impact of ulipristal on surgical outcomes.
- 7.2 The PBAC agreed there was a possible clinical place for ulipristal in short-term therapy prior to surgery. This was consistent with clinical advice received from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) who indicated that a three-month course of ulipristal has a possible clinical place as an oral alternative to GnRH analogues to reduce size of uterine fibroids prior to surgery.
- 7.3 The PBAC noted the sponsor's request in the Pre-PBAC response to remove the medium to long-term use of ulipristal from the proposed listing as the issues raised during the evaluation regarding the long-term (intermittent) use could not be adequately addressed in the response. The PBAC considered this appropriate and focused primarily on short-term treatment with ulipristal prior to surgery.
- 7.4 The PBAC considered that for short-term use of ulipristal in patients planning surgery, goserelin may be an appropriate comparator as it is used as an adjunct to surgery to facilitate the operative technique and reduce operative blood loss. However, the PBAC noted that goserelin is not PBS listed for use in uterine fibroids and the cost-effectiveness of goserelin for this indication has not been assessed. The PBAC noted the sponsor's agreement in the Pre-PBAC response (p2) with the ESC advice that surgery with no pre-treatment may also be an appropriate secondary comparator in this setting. The PBAC considered no treatment (or placebo) to be the appropriate main comparator, and that the comparison should include the impact of treatment on surgical outcomes.
- 7.5 The PBAC noted that there were no direct or indirect comparisons of ulipristal and goserelin from the clinical trial data. Given the differences between the studies presented, the PBAC agreed that this was not possible. The PBAC agreed with the evaluation that it was unclear how the studies were chosen for inclusion in the submission, as some studies of limited relevance were included while others were

excluded. The PBAC agreed with the ESC advice that the small number of goserelin studies provided in the submission, which were predominantly open-label trials, had insufficient detail to assess the risk of bias.

- 7.6 The PBAC considered there was insufficient evidence to make any conclusions regarding the comparative effectiveness and safety of the short-term use of ulipristal and goserelin prior to surgery. PEARL I and PEARL II demonstrated that ulipristal was superior to placebo and non-inferior to leuprorelin. The PBAC noted that there was no evidence of treatment-related differences in surgical outcomes provided, including the potential to allow less invasive surgical procedures. The PBAC noted ulipristal appeared to be well tolerated compared with leuprorelin, with patients in the ulipristal group displaying reduced progesterone levels and hot flushes.
- 7.7 The PBAC commented that while goserelin was not considered an appropriate comparator for medium to long-term use, the lack of evidence in this setting meant it was not possible to make any conclusions regarding the comparative effectiveness and safety of ulipristal and goserelin (with or without add-back therapy) in these clinical scenarios. The PBAC concluded that long-term data was required for a future resubmission if use of ulipristal in this setting is requested and this was supported by the RANZCOG advice. The PBAC noted that there are ongoing long-term studies being conducted in the European Union that may provide further safety data in the future.
- 7.8 The PBAC considered that a cost minimisation approach for ulipristal versus goserelin for the short-term and medium to long-term use was not appropriate as goserelin is not listed on the PBS for use in the treatment of uterine fibroids. Therefore, the cost-effectiveness of goserelin for this indication has not been assessed and as such a cost utility approach against no treatment would be more appropriate.
- 7.9 The PBAC agreed with the concerns raised by the DUSC regarding the financial estimates and noted that due to the limited epidemiological evidence available to inform the analysis, the estimated number of patients likely to be treated and, therefore, the estimated cost of ulipristal to the PBS/RPBS, was highly uncertain. The PBAC also agreed with the DUSC's comment that for the short-term pre-surgery population, where use of ulipristal would essentially be once in a lifetime treatment, an incidence approach, accounting for a prevalent pool in the first year, may be more appropriate. The PBAC considered that the PBS financial estimates should exclude cost offsets for goserelin, and that this increased the net cost to the PBS/RPBS in Year 5 from less than \$10 million to \$30 - \$60 million.
- 7.10 The PBAC considered that there was a possible clinical need for subsidised access to ulipristal for the short-term treatment of moderate to severe uterine fibroids prior to surgery and would welcome a major resubmission. The PBAC considered that a major resubmission should clearly define the clinical place for ulipristal. The resubmission would also need to include no treatment as a comparator and assess the impact of ulipristal treatment on surgical outcomes.
- 7.11 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

Vifor Pharma believes there is a clinical place for ulipristal acetate in the Australian healthcare system and will continue to present the available evidence to demonstrate the cost-effectiveness of treatment moderate to severe symptoms of uterine fibroids.