



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for ulipristal acetate

Proprietary Product Name: Esmya

Sponsor: Vifor Pharma Pty Ltd

**October 2016**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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# Contents

<b>About AusPARs</b>	<b>ii</b>
<b>Common abbreviations</b>	<b>5</b>
<b>I. Introduction to product submission</b>	<b>7</b>
Submission details	7
Product background	7
Regulatory status	8
Product information	9
<b>II. Quality findings</b>	<b>10</b>
Introduction	10
Drug substance (active ingredient)	10
Drug product	10
Biopharmaceutics	11
Quality summary and conclusions	12
<b>III. Nonclinical findings</b>	<b>13</b>
Introduction	13
Pharmacology	13
Pharmacokinetics	14
Toxicology	15
Nonclinical summary and conclusions	17
<b>IV. Clinical findings</b>	<b>18</b>
Introduction	18
Pharmacokinetics	20
Pharmacodynamics	21
Dosage selection for the pivotal studies	22
Efficacy	22
Safety	25
First round benefit-risk assessment	28
First round recommendation regarding authorisation	28
Clinical questions	28
Second round evaluation	29
Second round benefit-risk assessment	29
<b>V. Pharmacovigilance findings</b>	<b>30</b>
Risk management plan	30
<b>VI. Overall conclusion and risk/benefit assessment</b>	<b>38</b>
Quality	38

Nonclinical _____	38
Clinical _____	39
Risk management plan _____	42
Risk-benefit analysis _____	46
Outcome _____	47
<b>Attachment 1. Product Information _____</b>	<b>48</b>
<b>Attachment 2. Extract from the Clinical Evaluation Report _____</b>	<b>48</b>

## Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
AE	adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AUC	area under the plasma drug concentration-time curve
AUC <sub>t1-t2</sub>	area under the plasma drug concentration-time curve from t1 to t2
CHMP	Committee for Medicinal Products for Human Use
C <sub>max</sub>	maximum serum concentration of drug
CMI	Consumer Medicine Information
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
GnRH	Gonadotropin releasing hormone
IC50	inhibitory concentration 50%
MRI	magnetic resonance imaging
PAEC	PRM associated endometrial changes
PBAC	pictorial bleeding assessment chart
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
PR	progesterone receptor
PRM	progesterone receptor modulator
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	serious adverse event

Abbreviation	Meaning
SPRM	selective progesterone receptor modulator
$t_{1/2}$	elimination half life
Tmax	Time taken to reach the maximum concentration (Cmax)
TVUS	trans vaginal ultrasound
UA/UPA	ulipristal acetate

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	11 May 2016
<i>Date of entry onto ARTG</i>	17 May 2016
<i>Active ingredient:</i>	Ulipristal acetate
<i>Product name:</i>	Esmya
<i>Sponsor's name and address:</i>	Vifor Pharma Pty Ltd 80 Dorcas Street Melbourne VIC 3006
<i>Dose form:</i>	Uncoated oral tablet
<i>Strength:</i>	5 mg
<i>Container:</i>	Blister Pack of either PVC/PE/PVDC/AL or PVC/PVDC/AL
<i>Pack size:</i>	Cartons containing 28 and 84 tablets
<i>Approved therapeutic use:</i>	Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	5 mg/day
<i>ARTG number:</i>	237700

## Product background

This AusPAR describes the application by Vifor Pharma Pty Ltd<sup>1</sup> to extend the indications for ulipristal acetate (trade name, Esmya). Ulipristal acetate is a selective progesterone receptor modulator (SPRM or selective PRM), whose main pharmacodynamic action is to reversibly block the progesterone receptor in target tissues, including the uterus, ovaries and hypothalamus. Studies of PRMs for uterine fibroids date back 20 years. However, no other members of the class have been approved by TGA, FDA or EMA for any indications associated with uterine fibroids.

EllaOne (ulipristal 30 mg tablet) is registered in Australia (and EU, US, Canada) as a single dose for emergency contraception within 5 days of unprotected sexual intercourse or contraceptive failure. Therapy with Esmya involves a lower dose than with EllaOne, but a

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<sup>1</sup> On 27 May 2016, Esmya sponsorship was transferred to Vifor Pharma Pty Ltd from ERA Consulting (Australia) Pty Ltd.

longer treatment period (that is, 5 mg/day for recurring/intermittent 3 month/12 week treatment courses versus a single 30 mg dose).

The approved indication for ulipristal acetate 30 mg tablet (EllaOne) is:

*Emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.*

The proposed indication for Esmya 5 mg tablet is:

*Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.*

The proposed dosage and administration for Esmya ulipristal acetate 5 mg tablet is:

*The treatment consists of one tablet of 5 mg to be taken orally once daily for treatment courses of up to 3 months each. Long-term treatment has been studied up to 4 intermittent treatment courses.*

*Treatment courses should be intermittent. The treating physician should instruct the patient of the need of treatment free intervals. Re-treatment should start at the earliest during the second menstruation following the previous treatment course completion.*

*Treatment courses should always be started during the first week of menstruation.*

*If a patient misses a dose, the patient should take ulipristal acetate as soon as possible. If the dose was missed by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.*

Administration of PRMs (including ulipristal) causes a pattern of benign, nonphysiological, nonproliferative histologic changes in the endometrium termed PRM associated endometrial changes (PAEC).<sup>2</sup> These changes reverse spontaneously a few weeks to months after ceasing the PRM (including ulipristal). At present, there is no evidence to suggest that these changes increase the future risk of hyperplasia-with-atypia or endometrial carcinoma.

## Regulatory status

The international regulatory status at the time of submission is listed in Table 1.

**Table 1. International regulatory status at time of TGA submission.**

Country, date	Indications
EMA, Feb 2012	... pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to 3 months.  <i>(The 3-month limit was because of a lack of safety data beyond 3 months)</i>
EMA, Dec 2013	A second 3-month course was allowed (pre-operatively) if considered appropriate by the treating doctor.

<sup>2</sup> Mutter GL, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. *Mod Pathol.* 21: 591-8 (2008); Horne FM, Blithe DL. Progesterone receptor modulators and the endometrium: changes and consequences. *Hum Reprod Update* 13: 567-80 (2007); Williams AR, et al. Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. *Int J Gynecol Pathol.* 31: 556-569 (2012).



Country, date	Indications
EMA, Apr 2015	<p>... intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.</p> <p><i>(This allows for both pre-surgery medical treatment or repeated courses in women who are not planning or who wish to defer surgery.)</i></p>
Canada, Jun 2013	<p>Treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery. The duration of treatment is limited to 3 months.</p>
Canada, Dec 2015	<p>A second 3-month course was allowed (pre-operatively) if considered appropriate by the treating doctor.</p>

During the evaluation, TGA sought clarification from the sponsor as to whether the intention of the indications in Australia was to cover the 'double barrelled' indications in the EU. The sponsor replied:

*The applicant confirms that the proposed indication covers both pre-operative treatment and intermittent treatment for women or the physician to be able to choose the timing of surgery with flexibility, choose to differ surgery for a flexible period of time, or opt for medical treatment in case the woman does not wish to have surgery.*

During the evaluation, TGA asked the sponsor why Esmya had not been registered in the US. The sponsor provided the following response:

*Esmya is not yet registered in the US (the NDA not yet been submitted to the FDA), as US clinical studies to support the registration are on-going. Indeed, following discussions with the FDA regarding the development plan of Esmya, FDA requested additional US Phase III trial(s) to include American patients, as no US patients or sites were included in the EU Phase III studies.*

During the evaluation, TGA asked the sponsor why the indications for Esmya had not been extended to "intermittent use" in Canada. The sponsor provided the following response:

*Esmya has been granted initial Marketing Authorization in Canada in June 2013 for single course pre-operative treatment. The extension of indication to two 3-month courses has recently been approved by Health Canada (16th December 2015).*

An application to extend the indication to the intermittent use was submitted on 21 December 2015 and was under assessment at the time of TGA submission.

### Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Quality findings

### Introduction

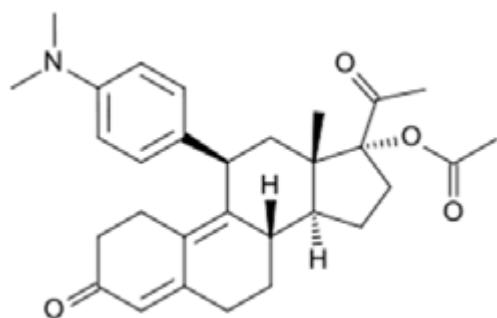
The proposed pack sizes are 28 and 84 tablet blister packs. This is different from the registered 30 mg EllaOne pack size (one tablet blister pack) due to the different PI dosage/administration and indications.

Ulipristal acetate drug substance and drug products are not subject to United States Pharmacopeia (USP), British Pharmacopoeia (BP), and the European Pharmacopoeia (Ph. Eur.) monographs.

### Drug substance (active ingredient)

Ulipristal acetate (Figure 1) is a white to yellowish crystalline powder that is freely soluble in dichloromethane, soluble in methanol, acetone and ethanol and insoluble in water. The drug substance used in this product is manufactured by the same manufacturer of ulipristal acetate that is used in the registered EllaOne 30 mg tablets.

**Figure 1. Chemical structure for ulipristal acetate.**



The manufacturing process yields a single crystalline form. The drug substance is micronised prior to use in the product to acceptable particle size distribution (PSD) specification limits.

These PSD limits, as well as other specification tests and limits, are the same as those previously approved by TGA for use in EllaOne 30 mg tablet.

The sponsor has provided assurance that the chemistry, manufacture, quality control and stability of the drug substance are the same as previously approved for EllaOne ulipristal acetate 30 mg tablet.

The manufacturing and quality control of the drug substance (including the drug substance specification) is acceptable.

### Drug product

The proposed drug product is a white to off-white round, biconvex uncoated tablet (with 7 mm diameter), containing 5 mg of ulipristal acetate and five other conventional excipients including microcrystalline cellulose, mannitol, croscarmellose sodium, talc and magnesium stearate. Each tablet is engraved on one face with "ES5". The drug product is intended for oral administration.

The product is to be supplied in two alternative blister packs (PVC/PE/PVDC/Al or PVC/PVDC/Al) in cartons of 28 and 84 tablets.

The quality of the product is controlled by acceptable specification that includes tests and limits for Appearance, Identification, Assay, Content Uniformity, Related Substances, Average Mass, Dissolution, Disintegration and Microbiological Quality.

The proposed release and expiry limits for two specified degradation products are the same as the limits approved in the previously assessed submission for EllaOne 30 mg tablet. These limits are acceptable. The proposed unspecified degradation product limit at release and expiry are in line with the ICH Q3B<sup>3</sup> identification threshold of 0.5% for the maximum daily dose of 5 mg. This is acceptable.

Dissolution test method and acceptance limit (Q = 75% in 30 minutes) have been adequately justified based on batch analyses of validation and clinical batches of the product.

The analytical methods used to analyse the product were adequately described and validated.

Acceptable GMP clearance was provided for the finished product manufacturer, but the GMP clearance for the drug substance manufacturer had expired in December 2015. This issue remains outstanding, but is expected to be resolved in due course.<sup>4</sup>

The stability data supplied supported a shelf life of 36 months for the unopened product (in both packaging materials) when it is stored below 30°C (inside the outer carton to protect from light).

## **Biopharmaceutics**

The company indicated that ulipristal acetate is a Biopharmaceutics Classification System (BCS) Class II drug substance (high permeability and low solubility). Five biopharmaceutical studies were provided in this submission. Four of these studies were previously assessed in the submission to register EllaOne 30 mg tablet.

The registered EllaOne 30 mg tablet is manufactured by wet granulation, which is a different method to that proposed for the 5 mg tablet (which is manufactured by direct compression). The corresponding strengths of ulipristal acetate (5 mg and 10 mg) tablets from these two manufacturing methods were compared in Study PGL09-004 and demonstrated to be bioequivalent.

Therefore, in this submission, the sponsor has presented bio-studies that used the 30 mg EllaOne (wet granulation) tablet to support the registration of the proposed 5 mg (direct compression) tablet, on the basis of the finding from the above study (PGL09-004) and the finding that ulipristal acetate has linear pharmacokinetics (from studies PGL09-004 and PGL09-023).

A summary of the biopharmaceutics studies is provided below.

- Study PGL-H-501 showed that ulipristal acetate is absorbed faster (although the difference is not statistically significant), and has a greater overall bioavailability following administration of the micronised tablet compared with the crystalline (non-micronised) capsule. Hence, the micronised form is used to manufacture this product and the 30 mg tablet.
- Based on the results from studies PGL09-004 and PGL09-023, the company has concluded that ulipristal acetate has been shown to have linear PK.

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<sup>3</sup> International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonised Tripartite Guideline: Impurities in New Drug Products Q3B(R2)", 2 June 2006.

<sup>4</sup> The renewed GMP clearance has been issued for the manufacture of ulipristal acetate drug substance (Expiry 11/08/2017). This issue is now resolved.

- The company has not performed an absolute bioavailability study for the 5 mg tablet, but has provided adequate justification for not doing so. The estimated absolute bioavailability of the 5 mg and 10 mg tablet is ~15%, based on the bioavailability results for EllaOne 30 mg tablet (Study PGL-H-650) and the linear PK assumption.
- Study PGL-H-512 (food effect) was performed using EllaOne 30 mg tablets. This study was evaluated in full. The study found that:
  - Administration with food slightly increased the overall bioavailability ( $AUC_{0-\infty}$ ) by on average 26%.
  - Absorption was somewhat delayed and more extended when administered with food, with a median  $T_{max}$  of 3.0 versus 0.75 h under fasting conditions, resulting in a mean decrease in  $C_{max}$  of 44%.
  - For metabolite Desmethyl Ulipristal Acetate (3877A), the results were comparable, with on average 19% higher  $AUC_{0-\infty}$  and 38% lower  $C_{max}$  when administered under fed compared with fasted conditions. The differences were statistically significant.
  - For EllaOne product (30 mg), these differences were acceptable from the clinical perspective, as the PI states that the product can be taken with or without food.
  - The sponsor has not performed additional food effect study for the proposed 5 mg tablet, but has provided further discussion to justify that the effect of food on the 5 mg tablet is expected to be similar that observed for the registered EllaOne 30 mg tablet.
  - The sponsor believes that the food effect is not expected to be of clinical relevance for this product. The food effect justification was brought to the attention of the Clinical Section for consideration whether the PI instruction that the tablets *may be taken with or without food* is appropriate

### Quality summary and conclusions

- There is one outstanding issue relating to the GMP clearance for the drug substance manufacturer. It is expected this issue will be addressed in due course, before the decision date. All other issues raised with the chemistry and quality aspects of the submission have been adequately resolved and these aspects are now acceptable.
- When the outstanding GMP issue has been satisfactorily resolved, then approval can be recommended with respect to chemistry and quality control.<sup>5</sup>
- There were biopharmaceutics issues that were brought to the attention of the Clinical Delegate for consideration on whether the food effect results are considered to be clinically relevant and whether the proposed instruction on the PI that the tablets may be taken with or without food is appropriate from a clinical perspective.
- The application has not been considered by the Pharmaceutical Subcommittee of the ACPM because no issues requiring their expertise were identified during the chemistry and quality evaluation.

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<sup>5</sup> The GMP issue has now been resolved and approval of registration can be recommended from a chemistry and biopharmaceutics perspective.

### III. Nonclinical findings

#### Introduction

Therapy with Esmya is to involve once daily oral administration of 5 mg ulipristal acetate for treatment courses of up to 3 months each. No maximum number of treatment courses is specified in the draft PI document, although reference is made to clinical studies that featured up to four treatment courses. The dose of ulipristal acetate with Esmya is lower than with the existing ulipristal acetate product, EllaOne (approved for use as an emergency contraceptive at a dose of 30 mg), but the treatment duration is longer (recurring 3 month treatment courses, compared with a single administration).

The submission contained studies that were submitted in the original application to register ulipristal acetate as a new chemical entity, plus a new study on tissue distribution (related to melanin binding). Data from the original application are considered here in terms of support for repeated dosing and to revise animal:human exposure margins achieved in the toxicity studies with respect to the new dose. As well, previously submitted data are considered with respect to the efficacy of ulipristal acetate in the new indication and regarding the potential for pharmacokinetic drug interactions in patients.

#### Pharmacology

##### Primary pharmacology

Ulipristal acetate binds with nanomolar affinity to progesterone receptors (PR-A and PR-B) to modulate progestin mediated functions. These functions include control of ovulation, implantation and maintenance of pregnancy (the basis for its use as an emergency contraceptive), as well as regulating the growth and differentiation of endometrial and myometrial tissues (of relevance to the proposed new indication).

Previously evaluated studies (included as secondary pharmacology data in the original submission) provide a pharmacological basis for the actions of ulipristal acetate against uterine fibroids. Uterine fibroids (or leiomyomas) are benign smooth muscle tumours of the myometrium that are associated with sex hormone dependent proliferation and mitotic activity.<sup>6</sup> The anti-proliferative activity of ulipristal acetate was investigated in vitro in cell culture studies measuring markers of proliferation and apoptosis. Human leiomyoma cells exposed to ulipristal acetate (0.01-1  $\mu$ M) showed concentration-dependent reductions in cell viability, and decreased expression of proliferating cell nuclear antigen (PCNA) and Bcl-2 protein levels.<sup>7</sup> Growth factors relevant to myometrial smooth muscle growth were also susceptible to modulation by ulipristal acetate. In experiments where normal human myometrial and leiomyoma cells were exposed to ulipristal acetate (0.01-1  $\mu$ M), treatment significantly reduced VEGF and adrenomedullin levels, and expression of their respective receptors VEGFR-1/2 and ADM receptor in leiomyoma cells only.<sup>8</sup> As well, ulipristal acetate reduced cell growth and proliferation in

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<sup>6</sup> Maruo T, et al. (2004) Sex steroidal regulation of uterine leiomyoma growth and apoptosis. *Human Reprod. Update*, 10: 207–220.

<sup>7</sup> Xu Q, et al. Progesterone receptor modulator CDB-2914 down-regulates proliferative cell nuclear antigen and Bcl-2 protein expression and up-regulates caspase-3 and poly(adenosine 5'-diphosphate-ribose) polymerase expression in cultured human uterine leiomyoma cells. *J. Clin. Endocrinol. Metab.* 90: 953-961 (2005).

<sup>8</sup> Xu Q, et al. Progesterone receptor modulator CDB-2914 down-regulates vascular endothelial growth factor, adrenomedullin and their receptors and modulates progesterone receptor content in cultured human leiomyoma cells. *Human Reprod. Update* 21: 2408-2416 (2006).

the human endometrial stromal cell line YHES.<sup>9</sup> Anti proliferative activity was also demonstrated for ulipristal acetate in vivo, with treatment with the drug reducing progesterone stimulated endometrial glandular proliferation in oestrogen primed rats and rabbits (Studies HRA2914-404 [PGL-H-404] and HRA2914-450 [PGL-H-450]). Apoptotic mechanisms were identified in the anti-proliferative actions of the drug, with elevated markers for apoptosis (caspase-3, cleaved poly[ADP ribose] polymerase) and actual apoptosis noted in ulipristal acetate treated leiomyoma cells.<sup>10</sup>

### **Secondary pharmacodynamics and safety pharmacology**

Ulipristal acetate has significant binding affinity for glucocorticoid receptors (GR), although functional assays revealed that the corresponding anti glucocorticoid activity is 36 times weaker than anti progesterone activity. Ulipristal acetate's action at glucocorticoid receptors is not anticipated to have implications or unintended actions relevant to the proposed new indication.

## **Pharmacokinetics**

### **Tissue distribution (melanin binding)**

Binding of drug related material to melanin was identified in a previously submitted study in rats conducted with <sup>14</sup>C ulipristal acetate, which featured observations up to 3 days post dose (Study HRA2914-425 [PGL-H-425]). A new tissue distribution study in pigmented rats utilised a longer observation period – up to 28 days post dose – to further examine the time-course for clearance from tissues (Study PGL09-019). High concentrations of radioactivity were seen in the uveal tract (a melanin containing tissue) at all time points, with no decline evident between Days 7-28 post dose. The level of radioactivity in the uveal tract/retina at Day 28 was almost 5 times greater than in the next highest tissue (liver). Retention/accumulation of drug-related material in melanin containing tissues does not appear to pose a safety concern though. No phototoxic potential was identified for ulipristal acetate in a standard in vitro assay (Neutral Red uptake in mouse 3T3 fibroblast cells; Study HRA2914-448 [PGL-H-448]) and no dermal or ocular toxicity was evident in repeat dose toxicity studies conducted in pigmented animals (rhesus and cynomolgus monkeys) where high multiples of the clinical exposure level were obtained.

### **Pharmacokinetic drug interactions**

Inhibitory activity against CYPs, P-glycoprotein and other transporters was investigated in previously evaluated studies. Based on these data, clinically significant inhibition of P-glycoprotein by ulipristal acetate is considered possible with dosing at 5 mg/day. The maximum expected concentration of the drug in the intestinal lumen on the apical side of enterocytes (4.2 µM; = 0.1 x 5 mg / 250 mL [calculated as described in published guidelines<sup>11</sup>]) is well above the IC<sub>50</sub> determined for inhibition of P-glycoprotein (0.732 µM [Study HRA2914-479 / PGL09-007]). While clinically significant inhibition of the intestinal BCRP transporter was predicted to be encountered in patients treated with 30 mg ulipristal acetate (as EllaOne), this is not expected with dosing at 5 mg per day with

<sup>9</sup> Wu Y, Guo SW. Inhibition of proliferation of endometrial stromal cells by trichostatin A, RU486, CDB-2914, N-acetylcysteine, and ICI 182780. *Gynecol. Obstet. Invest.* 62: 193-205 (2006).

<sup>10</sup> Xu Q, et al. Progesterone receptor modulator CDB-2914 down-regulates proliferative cell nuclear antigen and Bcl-2 protein expression and up-regulates caspase-3 and poly(adenosine 5'-diphosphate-ribose) polymerase expression in cultured human uterine leiomyoma cells. *J. Clin. Endocrinol. Metab.* 90: 953-961 (2005); Wu Y, Guo SW. Inhibition of proliferation of endometrial stromal cells by trichostatin A, RU486, CDB-2914, N-acetylcysteine, and ICI 182780. *Gynecol. Obstet. Invest.* 62: 193-205 (2006).

<sup>11</sup> European Medicines Agency, "Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2\*\*)", 21 June 2012.

this product (based on the maximum concentration in the intestinal lumen being at least 2 fold lower than the drug's IC<sub>50</sub> at the transporter [4.2 µM compared with an IC<sub>50</sub> of 8.92 µM]).

## Toxicology

Previously submitted studies established that ulipristal acetate has a low order of acute toxicity by the oral route. Pivotal repeat dose toxicity studies were conducted in rats and cynomolgus monkeys, and involved daily oral administration for up to 6 months and 9 months in the respective species. In accordance with published guidelines,<sup>12</sup> the duration of these studies is sufficient to support chronic human administration. Only female animals were used, which is acceptable given the indication.

The effects of ulipristal acetate were generally directed to reproductive tissues (ovaries and uterus), with less prominent changes in mammary tissue, adrenal glands, liver and pituitary gland also seen. The effects observed were similar to those seen with mifepristone (progesterone receptor antagonist), and consistent with the drug's progesterone modulating and anti-glucocorticoid activities. The endometrial findings are of note and are briefly discussed below.

## Relative exposure

Animal:human exposure ratios for ulipristal acetate, based on plasma AUC or – in the absence of suitable toxicokinetic data – body surface area adjusted doses, have been revised from those calculated in the original nonclinical evaluation report to reflect the new human dose of 5 mg/day. No human AUC data for a repeated 5 mg/day dose were provided by the sponsor. Instead, the human reference AUC value used here has been derived by halving the steady state value for dosing at 10 mg/day (Clinical Study PGL09-023). Considering that AUC in humans in the study was supra dose proportional, this is a conservative extrapolation (overestimating human exposure, and consequently underestimating animal:human exposure multiples). Exposure ratios calculated for this product are ~5-times higher than those for EllaOne based on AUC (human AUC<sub>0-24 h</sub> after a single 30 mg dose, 0.556 µg·h/mL) and 6 times higher based on body surface area.

**Table 2. Estimated relative exposure to ulipristal acetate in selected toxicity studies.**

Species	Study duration	Dose		AUC <sub>0-24 h</sub> (µg·h/mL)	Exposure ratio <sup>#</sup>	
		mg/kg/day	mg/m <sup>2</sup> /day		AUC	BSA
<i>Pivotal repeat dose toxicity</i>						
Rat (SD)	6 months	1	6	–	–	1.8
		5	30	3.65	34	9
		25	150	29.8	276	45
Monkey	6 months;	1	12	–	–	3.6

<sup>12</sup> European Medicines Agency, "ICH Topic M 3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, Step 3: Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (CPMP/ICH/286/95)", July 2008.

Species	Study duration	Dose		AUC <sub>0-24h</sub> ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	Exposure ratio <sup>#</sup>	
		mg/kg/day	mg/m <sup>2</sup> /day		AUC	BSA
(Cynomolgus)	9 months	5	60	0.026*	0.24	18
		25	300	0.511*	4.7	91
<b><i>Carcinogenicity (NOELs)</i></b>						
<b>Mouse</b> (TgRasH2)	26 weeks	130	390	67.8	628	118
<b>Rat</b> (SD)	2 years	10	60	14.6	135	18
<b><i>Reproductive toxicity</i></b>						
<b>Rat</b> (SD)	Male fertility	10	60	-	-	18
	Embryofetal development	0.1	0.6	-	-	0.18
		0.3	1.8	-	-	0.5
		1	6	-	-	1.8
	Pre/post natal development	0.03	0.18	-	-	0.05
		0.1	0.6	0.004	0.04	0.18
		0.3	1.8	0.023	0.21	0.5
<b>Rabbit</b> (NZW)	Embryofetal development	0.1	1.2	-	-	0.36
		0.3	3.6	-	-	1.1
		1	12	-	-	3.6
<b>Guinea pig</b> (unknown strain)	Pregnancy maintenance <sup>a</sup>	6	S C	48	-	15
		20		120	-	36
		60		480	-	145
<b>Monkey</b> (Cynomolgus)	Pregnancy maintenance <sup>b</sup>	0.5	6	-	-	1.8
		5	60	-	-	18
<b>Human</b> (healthy female volunteers)		[5 mg]	3.3	0.108 <sup>†</sup>	-	-

# = animal:human plasma AUC or doses adjusted for body surface area (BSA), based on mg/kg to mg/m<sup>2</sup> conversion factors of 3 (mouse), 6 (rat), 12 (rabbit), 8 (guinea pig), 12 (monkey) and 33 (human; 50 kg



body weight assumed) AUC<sub>0-24 h</sub> data shown for the pivotal rat study were obtained after a single dose in Study HRA2914-421

\* = AUC<sub>0-24 h</sub> values shown for monkeys have been derived from AUC<sub>0-270d</sub> values and are unreliable due to sparse sampling

a = Study HRA2914-407,<sup>13</sup> 500 g animal body weight assumed

b = Study HRA2914-409<sup>14</sup>

† = halved from the AUC<sub>0-24 h</sub> value reported for humans at 10 mg/day at steady state in Study PGL09-023

In the 9 month study in monkeys, uterine cystic endometrial hyperplasia with squamous metaplasia, cystic dilatation and endometrial thickening occurred at all dose levels tested (1-25 mg/kg/day). The findings were seen to be reversible. In monkeys treated for 6 months, cystic dilatation was seen in almost all animals treated at 5 or 25 mg/kg/day, with mild squamous metaplasia observed in one high-dose animal. The pivotal 6 month study in rats established a No Observed Effect Level (NOEL) of 5 mg/kg/day for microscopic changes in the uterus; glandular dilatation (minimal to mild) was evident at 25 mg/kg/day. There were no preneoplastic lesions in the chronic repeat dose toxicity studies. Carcinogenicity studies with ulipristal acetate, involving once daily oral administration in rats (for 2 years) and transgenic mice (6 months), were submitted in the original application to register ulipristal acetate. Neither study revealed a treatment related increase in tumours (nor pre neoplastic lesions) at large margins of the human exposure.

The reproductive toxicity of ulipristal acetate was examined in previously evaluated studies. With regard to effects on female fertility, inhibition of ovulation and prevention of pregnancy were shown in multiple laboratory animal species. Male fertility was unaffected in rats. In conventional embryofetal development studies in rats and rabbits, ulipristal acetate increased post implantation loss (due to increased early resorptions) and decreased live litter size at 1 mg/kg/day, occurring in the absence of maternotoxicity. This dose is a low multiple of the human dose based on body surface area, but toxicokinetic data obtained in the pre/postnatal development study suggest that actual exposure (plasma AUC) was subclinical in rats. Doses tested were low in order to maintain pregnancy. There was no evidence of teratogenicity in any surviving offspring in either species. Abortions and still births were seen in other studies in rats ( $\geq 0.3$  mg/kg/day), guinea pigs and monkeys. The draft PI includes pregnancy as a contraindication for Esmya. This is appropriate.

### Pregnancy category

The sponsor proposes Pregnancy Category D.<sup>15</sup> This is considered appropriate. It matches the existing categorisation for EllaOne, and is consistent with findings of embryofetal lethality in multiple laboratory animal species.

### Nonclinical summary and conclusions

- Esmya is proposed to be used for the treatment of uterine fibroids. Therapy with Esmya involves a lower dose than with EllaOne but a longer treatment period (that is, 5 mg/day for recurring 3 month treatment courses compared to a single 30 mg dose).

<sup>13</sup> Poyser NL, Forcelledo ML. A comparison of the pregnancy-terminating potencies of three anti-progestins in guinea pigs and the effects of sulprostone. *Prostaglandins Leukotrienes and Essential Fatty Acids* 50: 245-247 (1994).

<sup>14</sup> Tarantal AF, et al. Effects of two antiprogestins on early pregnancy in the long-tailed macaque. *Contraception* 54: 107-115 (1996).

<sup>15</sup> Pregnancy Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

- The nonclinical assessment is mostly made based on data that was submitted in the original application to register ulipristal acetate as a new chemical entity. The current submission contained one new study (on tissue distribution).
- Pharmacology studies showing concentration dependent reductions in markers for proliferation, growth factors and cell viability, and increased apoptosis in human cultured leiomyoma cells exposed to ulipristal acetate, and anti proliferative activity in vivo in the rat and rabbit endometrium, support the product's use for the proposed indication.
- Binding to melanin was identified previously. A new tissue distribution study in rats further supports the potential for retention/accumulation of drug related material in pigmented tissues. Despite this, phototoxicity and repeat dose toxicity studies do not indicate any resultant toxicity.
- Chronic administration of ulipristal acetate produced histopathological changes in the endometrium of monkeys, comprising endometrial thickening, cystic endometrial hyperplasia, squamous metaplasia and cystic dilatation. This occurred at all dose levels tested, and the changes were reversible when ulipristal acetate treatment was withdrawn. These findings may be clinically relevant, dependent on the pattern of use.
- Ulipristal acetate was shown not to be carcinogenic in studies in rats and transgenic mice.
- Embryofoetal lethality by ulipristal acetate has been demonstrated in multiple laboratory animal species at low or subclinical exposure levels. The sponsor proposes contraindication in pregnancy and assignment to Pregnancy Category D, which is supported.
- Overall, there are no nonclinical objections to the registration of Esmya.

## IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### Introduction

#### Clinical rationale

Uterine fibroids (myomas, leiomyomata) are benign, monoclonal tumours of the myometrium. Uterine fibroids are the most common gynaecological tumour in pre-menopausal women, reported to occur in up to 70% of Caucasian women by age 50 years<sup>1</sup> with a peak incidence at 40-50 years of age. Risk factors for the development of uterine fibroids include nulliparity, obesity, polycystic ovarian syndrome, hypertension, Afro-Caribbean descent and family history of fibroids. Leiomyomata are under the influence of oestrogen and progesterone, and mostly regress after menopause.

Uterine fibroids vary in size and location (submucosal, intramural, or subserosal) and can be single or multiple. While the majority of fibroids are asymptomatic and followed without intervention, up to 50% of women with uterine fibroids have symptoms, most commonly heavy uterine bleeding. Other presentations can include bulk symptoms (pelvic pressure, urinary urgency and frequency), iron deficiency anaemia and subfertility.

Treatment options are based on symptoms, age, reproductive considerations, size and location of myomas. Surgical management is the mainstay of treatment for uterine fibroids. In Australia, uterine fibroids are one of the most common indications for

hysterectomy,<sup>16</sup> the definitive procedure for fibroids. Uterus preserving surgical options include myomectomy, uterine artery embolisation and endometrial ablation.

Currently, there are no effective long term, non surgical treatment options for of uterine fibroids. Whilst GnRH agonists are effective prior to fibroid surgery in reducing fibroid volume and aiding correction of anaemia, longer term use is limited due to menopausal symptoms and bone demineralisation resulting from the suppression of oestrogen to castration like levels. In Australia, the GnRH agonist goserelin 3.6 mg implant is approved for the management of uterine fibroids as an adjunct to surgery for a period of 3 to 6 months. The registered indication is:<sup>17</sup>

*In the management of fibroids, Zoladex shrinks the lesions and reduces the symptoms, including pain. Zoladex also increases the haemoglobin concentration and haematocrit in women with anaemia attributable to menorrhagia. It is used as an adjunct to surgery to facilitate the operative technique and reduce operative blood loss.*

Hormonal therapies, such as combined hormonal contraceptives and progestational agents, are used for symptomatic management of heavy uterine bleeding, but are not considered effective in the treatment of uterine fibroids. The levonorgestrel releasing intra uterine device (Mirena) is widely used for the control of heavy menstrual bleeding, however, is contraindicated if the uterine cavity is distorted by fibroids<sup>18</sup> and there are suggestions in the literature that expulsion rates may be higher in the presence of submucosal fibroids.<sup>19</sup>

Ulipristal acetate is a SPRM. The sponsor states by acting as a progesterone receptor antagonist, ulipristal deprives the uterine fibroids of growth stimulation due to progesterone, and can induce amenorrhoea by interacting with progesterone receptors on the endometrium. Further, the sponsor states ulipristal acetate will provide an alternative treatment option to surgery, or short term GnRH agonist use, for the management of uterine fibroid symptoms over a longer period of time. The clinical rationale is considered acceptable.

### Contents of the clinical dossier

The clinical dossier contained:

- 24 clinical pharmacology studies, including 17 that provided pharmacokinetic data and 7 that provided pharmacodynamic data
- 6 efficacy and safety studies: PGL11-006, PGL09-026 and extension PGL09-027 and PGL11-024, PGL07-021, PGL07-022
- 2 Phase II studies: PGL-N-0090 and PGL-N-0287
- 5 Periodic Safety Update Reports (PSURs), literature references

### Paediatric data

The submission did not include paediatric data. The sponsor states the EMA granted a paediatric investigation plan (PIP) waiver for girls from age menarche to less than 18 years.

<sup>16</sup> Varol N, et al. Ten-year review of hysterectomy morbidity and mortality: can we change direction? *Aust NZ J Obstet Gynaecol.* 41: 295-302 (2001).

<sup>17</sup> Australian PI Zoladex 3.6 mg Implant.

<sup>18</sup> Australian PI Mirena.

<sup>19</sup> Ikomi A, Pepra EF. Efficacy of the levonorgestrel intrauterine system in treating menorrhagia: actualities and ambiguities. *J Fam Plann Reprod Health Care* 28: 99-100 (2002).

## Good clinical practice

The sponsor states all trials were performed in accordance with the principles of Good Clinical Practice.

## Pharmacokinetics

### Studies providing pharmacokinetic data

Table 4 shows the studies relating to each pharmacokinetic topic. The majority of these studies have been submitted previously to TGA. Study summaries are provided for those studies evaluated in this submission.

**Table 4. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	PGL-H-512 (HRA2914-512) <sup>a</sup> PGL-H-501 (HRA2914-501) <sup>a</sup> PGL-H-503 (HRA2914-503, Passaro et al., 2003) <sup>a</sup> PGL-H-504 (HRA2914-504) <sup>a</sup> PGL09-015 (HRA2914-553) <sup>a</sup>
	- Multi-dose	PGL09-023 (HRA2914-545) <sup>a</sup>
	Bioequivalence† - Single dose	PGL-H-516 (HRA2914-516) <sup>a</sup> PGL09-004
	- Multi-dose	PGL-H-650 (HRA111014-001) <sup>a</sup>
	Food effect	PGL-H-512 (HRA2914-008) <sup>a</sup>
PK in special populations	Target population § - Single dose	Nil
	Hepatic impairment	PGL-W-001
	Renal impairment	Nil
	Elderly	Nil
Genetic/gender related PK	Lactating females	PGL-H-514 (HRA2914-514) <sup>a</sup>
PK interactions	Erythromycin	PGL-09-022 (HRA2914-549) <sup>a</sup>
	Esomeprazole	PGL11-002 (HRA2914-546) <sup>a</sup>
	Fexofenadine	PGL-W-002 (HRA2914-548) <sup>a</sup>
	Ketoconazole	PGL-W-003 (HRA2914-547) <sup>a</sup>

PK topic	Subtopic	Study ID
	Rifampicin	PFL-H-551 (HRA2914-551) <sup>a</sup>

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

a Evaluated in the UPA (EllaOne) submission.<sup>20</sup>

The TGA Clinical Evaluator for the original marketing authorisation application stated none of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

### Evaluator's conclusions on pharmacokinetics

The majority of studies regarding the PKs of UPA have been previously evaluated by the TGA in the original marketing authorisation. The Clinical Evaluator for this submission concluded the PKs for UPA to have been adequately described for the target population (women of child bearing potential) and this argument is endorsed by the EMA Evaluator for UPA 5 mg.

Study PGL-W-001 was not considered conclusive regarding use in moderate hepatic impairment due to markers for same deemed inadequate. The PI recommends no dosage adjustment in mild hepatic impairment, with use in moderate and severe hepatic impairment not recommended unless the patient is closely monitored. The EMA Evaluator considers this recommendation justified although did not consider a strict contraindication necessary as UPA "is not a substance with a narrow therapeutic window and 10-fold higher doses (50 mg/day) have been administered without serious safety concerns." This Evaluator agrees with this comment.

There were no studies in patients with renal impairment. As such, UPA 5 mg is not recommended in patients with severe renal impairment unless closely monitored.

### Pharmacodynamics

#### Studies providing pharmacodynamic data

Table 5 shows the studies relating to each pharmacodynamic topic.

**Table 5. Submitted pharmacodynamic studies.**

PD Topic	Subtopic: Study ID
Primary Pharmacology	Effect on luteolysis: PGL-H-503 (HRA2914-503), Passaro <i>et al.</i> , 2003 <sup>a</sup>
	Effect on folliculogenesis: PGL-H-505 (HRA2914-505) <sup>a</sup>
	Effect on menstrual cycle: PGL-H-506 (HRA2914-506) <sup>a</sup>
	Effect on ovulation:
	PGL-H-554 (HRA2914-554) <sup>a</sup>
	PGL-H-510 (HRA2914-510) <sup>a</sup>
	PGL-P-349
	Effect on follicle rupture: PGL-H-511 (HRA2914-511) <sup>a</sup>

<sup>20</sup> Passaro MD, et al. Luteal phase dose-response relationships of the antiprogesterin CDB-2914 in normally cycling women. *Hum Reprod.* 18: 1820-1827 (2003).

<sup>a</sup> Evaluated in the UPA (EllaOne) submission.<sup>21</sup>

The TGA Clinical Evaluator of the original marketing authorisation submission stated none of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

### Evaluator's conclusions on pharmacodynamics

The Clinical Evaluator for this submission stated the PD studies examined the ulipristal dose range 10-200 mg as a single dose, and concluded there were dose dependent effects in follicular growth, follicular rupture, endometrial growth and cycle length, although states these effects were not significant at the 10 mg dose level.

### Dosage selection for the pivotal studies

Regarding dose selection for pivotal study PGL11-006, the sponsor states both the 5 mg and 10 mg doses of UPA demonstrated efficacy over a single 3 month treatment course; it was hypothesised the 10 mg dose may be advantageous in repeated intermittent administration.

A dose of UPA 10 mg daily was used in Study PGL09-027 (commenced prior to Study PGL11-006). The sponsor states the results of the short term studies PGL07-021 and PGL07-022, using both 5 mg and 10 mg UPA doses, were not known at the time of study design of PGL09-026 and PGL09-027, and the 10 mg dose was chosen as:

*as it was hypothesised that a 10 mg dose might have advantages in terms of efficacy for a repeated intermittent treatment.*

### Efficacy

#### Studies providing efficacy data

There are five Phase III studies provided in the dossier. The two studies PGL11-006 and PGL09-027 (extension of PGL09-026) are considered pivotal as these two studies provide data for long-term administration of UPA for uterine fibroids. Studies PGL07-021, PGL07-022, and PGL09-026 provide data for short term (3 month) pre operative use of UPA and are considered supportive. A summary of the key study design parameters for the Phase III studies is shown below in Table 6.

**Table 6. Summary of Phase III studies key design parameters**

Phase III Study	Design	Duration	N	Dose of UPA	Age range	Key demographics / disease characteristics	Key inclusion criteria
PGL11-006	Double-blind, parallel-group	4 x 84 days	4 5 1	5 mg (n= 228) or 10 mg (n= 223) daily	18-50 inclusive	94.2% white; mean age 41.5 years; mean BMI 25.2; 94.7% of child-bearing	PBAC score > 100, myomatous uterus < 16 weeks, largest

<sup>21</sup> Passaro MD, et al. Luteal phase dose-response relationships of the antiprogesterin CDB-2914 in normally cycling women. *Hum Reprod.* 18: 1820-1827 (2003).

Phase III Study	Design	Duration	N	Dose of UPA	Age range	Key demographics / disease characteristics	Key inclusion criteria
						potential; mean (median) PBAC score > 100 at screening	fibroid 3-12 cm diameter inclusive
PGL09-026	Open-label for UPA	90 days	209	10 mg daily	18-48 inclusive	85.1% white; mean age 40.0 years; mean BMI 25.4; 96.0% of child-bearing potential; mean (median) PBAC score at baseline = 319 (216).	myomatous uterus < 16 weeks, at least one myoma ≥ 3 cm diameter, nil larger than 10 cm, eligible for hysterectomy or myomectomy.
PGL09-027 (extension of PGL09-026)		Further 3 x 90 day courses	132				
PGL07-021	Double-blind, placebo controlled	13 weeks	194	5 mg (n= 96) or 10 mg (n= 98) daily	18-50 inclusive	88.0% white; mean age 41.6 years; mean BMI 25.3; 92.1% of child-bearing potential; mean (median) PBAC score at baseline = 452 (361).	PBAC score > 100, myomatous uterus ≤ 16 weeks gestation equivalent, at least one myoma ≥ 3 cm diameter, nil larger than 10 cm, fibroid related anaemia defined as Hb ≤ 10.2g/dL, eligible for surgery.
PGL07-022	Double blind, double dummy, active comparator controlled	13 weeks	307	5mg (n= 102) or 10 mg (n= 103) daily	18-50 inclusive	Mean age 40.4 years; mean BMI 25.5; 96.3% of child-bearing potential; mean (median)	PBAC score > 100, myomatous uterus ≤ 16 weeks gestation equivalent, at least one

Phase III Study	Design	Duration	N	Dose of UPA	Age range	Key demographics / disease characteristics	Key inclusion criteria
	(leuprorelin)					PBAC score at baseline = 370 (282)	myoma $\geq$ 3 cm diameter, nil larger than 10 cm, eligible for surgery.

The pictorial bleeding assessment chart (PBAC) is a validated scoring method to objectively measure menstrual blood loss, and was used as a measure of uterine bleeding for the key efficacy endpoints in the Phase III studies. Heavy bleeding is defined as PBAC > 100 (equivalent to over 80 mL blood loss).

Fibroid and uterine volumes were assessed by trans vaginal ultrasound (TVUS) in all Phase III studies, except for Study PGL-021, where MRI was the imaging modality of choice. The sponsor states ultrasound is the routine investigation of choice in patients presenting with heavy uterine bleeding/fibroids, however MRI is more precise with regard to measurements of fibroids and was used in Study PGL07-021 as change in total fibroid volume was a co-primary endpoint. The sponsor states this was based on discussions with various EU regulators.

#### Evaluator's conclusions on efficacy

Data for up to 4 repeated treatment courses with UPA has been provided in the long-term study PGL11-006, as well as Study PGL09-027. The EMA Evaluator noted the inclusion and exclusion criteria for Study PGL11-006 were acceptable and generally consistent with those of previous studies, except that eligibility for surgery was not a requirement.

Demographics were similar across the Phase III trials, with the patient population mostly white, of child-bearing potential and aged approximately 40; these demographic parameters are considered largely consistent with the target therapeutic population in Australia.

This Evaluator agrees with the EMA Evaluator the efficacy endpoints used in the clinical trials were clinically relevant (assessment of bleeding, myoma volume, pain and quality of life assessments). There were differences observed between the 5 mg group and 10 mg ulipristal groups for the primary endpoint (percentage of subjects in amenorrhoea) in the pivotal Study PGL11-006, although this was considered a rather strict endpoint as discussed in the Evaluator comments. When taking into consideration other bleeding pattern endpoints, such as controlled bleeding (no episodes of heavy bleeding and maximum 8 days if bleeding over 56 days) and the median time to amenorrhoea, the results between the 5 mg and 10 mg UPA groups were similar. Sustained improvements in bleeding pattern profile endpoints were evident after consecutive courses of UPA.

Additional supportive evidence was provided in the short term studies, with over 90% of subjects in the ulipristal groups with PBAC scores < 75 (considered consistent with normal menstrual blood loss) after a single treatment course. Further proof of efficacy was demonstrated by reduction in fibroid volume, uterine volume as well as improvement in pain and quality of life assessment scores, which were maintained with repeat treatment courses in the long term studies. The results for these parameters were generally similar between the 5 mg and 10 mg UPA groups. Statistically significant improvement over



placebo was noted in the short term study PGL07-021 for the co-primary endpoints (for reduction in uterine bleeding and change in total myoma volume). There are no long term comparator products available, and the active comparator used in the short term study is not registered for use in fibroids in Australia.

## **Safety**

### **Studies providing safety data**

There are safety data for UPA available from the 5 Phase III Studies:

- 2 long term studies: PGL11-006 and PGL09-027
- 3 short term studies: PGL07-021, PGL07-022 and PGL07-026

Further, safety data are available from 2 Phase II studies (PGL-087 and 0090), as well as 28 studies conducted in healthy female subjects as part of the development program for emergency contraception. Additional safety data has been evaluated in the original marketing authorisation application for UPA 30 mg (EllaOne).

### ***Pivotal efficacy studies***

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs)
- AEs of special interest (AESI), including reproductive and breast disorders, endometrial safety.
- Laboratory tests, including endocrine parameters

### **Patient exposure**

The sponsor states there have been over 6200 subjects exposed to ulipristal during the clinical development program (as emergency contraception and as a treatment for uterine fibroids). In particular, 6168 subjects have been exposed to a dose of UPA  $\geq$  5 mg or above (any duration), 4999 subjects received a single dose, and 1238 subjects have received repeated doses of UPA.

Of the 1238 subjects receiving multiple doses of UPA:

- 1053 have been exposed to dose of UPA  $\geq$  5 mg for  $\geq$  3 months.
- 551 have been exposed to dose of UPA  $\geq$  5 mg for  $\geq$  two 3 month courses (stated to equate to 9 months when including off treatment intervals).
- 457 have been exposed to UPA 5 mg or 10 mg for four 3 month courses (stated to equate to 21 months when including off treatment intervals).

The following table was provided.

**Table 7: Phase III repeated dose studies with ulipristal acetate in subjects with symptomatic uterine fibroids (safety population).**

Study	Design	Ulipristal acetate		Control		Planned Duration of treatment	Overall treatment + follow-up period
		5 mg/day	10 mg/day	Placebo	Active control		
		Number of subjects					
PGL07-021	Double-blind, placebo controlled	95	98	48	-	12 weeks	3 + 6 months
PGL07-022 <sup>a</sup>	Double-blind, double-dummy, active comparator controlled	97	103	-	101	12 weeks	3 + 6 months
PGL09-026	Open-label	-	209	-	-	12 weeks	3 + 3 months
PGL09-027	Open-label	-	132 <sup>b</sup>	-	-	Up to 3 additional courses of 12 weeks <sup>c</sup>	Approx. 18 + 3 months
PGL11-006	Double-blind, parallel groups	230	221	-	-	4 courses of 12 weeks <sup>d,e</sup>	Approx. 12 months

a. Protocol specified two co-primary safety endpoints.

b. 132 subjects (from the PGL09-026 population) were included in the safety population, but only 131 received ulipristal acetate during Study PGL09-027 (1 subject received placebo [double blind treatment] only instead of ulipristal acetate).

c. Each course separated by 10 days of treatment with placebo or progestin [NETA] followed by a drug-free period.

d. Each course separated by a drug-free period until the start of the second menstruation following the end of the previous treatment course.

e. Study PGL11-006 comprises a total of four 3 month treatment courses: at time of preparation of this summary, 369 and 271 subjects have completed 3 and 4 treatment courses, respectively.

### Post marketing data

There were 5 PSUR documents provided and progress report for the post authorisation safety study PGL10-014. Key findings of the PSURs are discussed below. In summary, there were no new safety issues identified and no regulatory action taken for safety reasons.

- PSUR number 5 covers the period 23 February 2014 to 22 August 2014.
  - interval marketing exposure was estimated at approximately 47,300 patients.
  - cumulative marketing exposure was estimated at around 107,500 patients.
  - there were no cases of liver toxicity in clinical trials; there was 1 report from a spontaneous source, but not qualifying as drug induced liver injury.
  - no cases ‘inappropriate management of endometrium thickening’ or ‘inappropriate diagnosis of endometrial hyperplasia’ was received from clinical trials and other sources were not conclusive.
- PSUR number 4 covers the period 23 August 2013 to 22 February 2014.
  - interval marketing exposure was estimated at around 32,700 patients.
  - cumulative marketing exposure was estimated at around 60,500 patients
  - there were no safety issues identified.
- PSUR number 3 covers the period 23 February 2013 to 22 August 2013.

- interval marketing exposure was estimated at approximately 14,500 patients.
- cumulative marketing exposure was estimated at around 27,800 patients.
- there was 1 case each of ‘inappropriate management of endometrium thickening’ and ‘inappropriate diagnosis of endometrial hyperplasia’. The Sponsor states the educational programme (Physician’s Guide to Prescribing and Pathologists brochure) was implemented in countries where Esmya is marketed).
- two cases of potential liver toxicity were received; neither confirmed the important potential risk of ‘drug induced liver injury’.
- PSUR number 2 covers the period 23 August 2012 to 22 February 2013.
  - interval marketing exposure was estimated at approximately 8,500 patients.
  - cumulative marketing exposure was estimated at approximately 12,900 patients.
  - there was 1 case of ‘inappropriate management of endometrium thickening’.
- PSUR number 1 covers the period 23 February 2012 to 22 August 2012.
  - 5,500 patients were exposed to Esmya during the review period.
  - There were no new relevant safety findings identified.

Study PGL10-014 is a multicentre, prospective, non-interventional study of women treated with UPA 5 mg as pre-operative treatment of moderate to severe symptoms of uterine fibroids. There are 1568 patients enrolled; patients will be followed up during treatment and for up to 12 months following treatment discontinuation, for a total of up to 15 months follow up. In the second yearly progress report (dated 9 May 2014, covering the period 24 May 2012 to 15 April 2014) the sponsor stated 1546 patients enrolled at the cut-off, with 936 patients have had at least one post baseline visit; there have been no safety concerns identified at the time of the report.

### **Evaluator’s conclusions on safety**

The safety profile for UPA has been well described in the data provided. Overall, UPA is generally well tolerated; the most common AEs were headache and hot flush, most of which were mild or moderate in intensity. Further, in the long term studies, adverse events were more common during the first treatment course than in subsequent treatment courses.

The main safety issue identified related to endometrial safety. Concerns raised by the CHMP during the EMA evaluation process are considered to have been adequately addressed by the EMA assessor in the response to further information sought by the CHMP. The EMA evaluator concluded:

*Based on the available data related to endometrial safety after up to 4 treatment courses, no increased occurrence of more serious conditions of the endometrium such as hyperplasia with atypia or endometrial carcinoma was observed. The final study report from Study PGL11-006 did not reveal any unexpected safety findings. It is reassuring that median endometrium thickness (7-8 mm) was similar to screening levels at all-time points during study and during the post treatment follow up.*

This evaluator endorses these comments. There have been no additional safety concerns identified in the available post marketing data.

## **First round benefit-risk assessment**

### **First round assessment of benefits**

The benefits of ulipristal in the proposed usage are:

- There is a lack of available long term medical treatment options in Australia for women with symptomatic uterine fibroids.
- Clinically relevant improvement in bleeding profile as well as reductions in myoma volume, uterine volume and improvement in quality of life parameters have been demonstrated with up to 4 repeated intermittent courses of ulipristal acetate.

### **First round assessment of risks**

The risks of ulipristal in the proposed usage are:

- Endometrial safety: potential identified risks include changes in endometrial thickness, and endometrial hyperplasia. Concerns regarding these issues have been addressed during the EMA evaluation. The EMA Evaluator noted frequency of endometrial hyperplasia was low in the pivotal study and there were fewer subjects with endometrial thickness > 16 mm with successive treatment courses. Further, the frequency of PAEC did not increase with repeated treatment courses, and rapid reversibility of these changes was observed following treatment completion and subsequent menstruation.
- There are no long term follow up data following repeated intermittent course of ulipristal acetate to ascertain the sustainability of treatment effect, and long term safety issues.

### **First round assessment of benefit-risk balance**

The benefit-risk balance of ulipristal acetate 5 mg, given the proposed usage, is uncertain at this point in time. The benefit-risk balance will be discussed at Round 2.

### **First round recommendation regarding authorisation**

Recommendation regarding authorisation will be made at Round 2.

### **Clinical questions**

1. The proposed PI contains the following information regarding endometrial changes in the Precautions section:
  - Reversible increase in thickness of the endometrium may occur under treatment. If the endometrial thickening persists after return of menstruations during off treatment periods or beyond 3 months following the end of treatment courses, it may need to be investigated as per usual clinical practice to exclude other underlying conditions.
  - In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off treatment period. In case of persistent thickening of the endometrium and/or an altered bleeding such as inter menstrual bleeding, investigation including endometrial biopsy should be performed in order to exclude other underlying conditions.

- In case of hyperplasia (without atypia), monitoring as per usual clinical practice (for example, a follow up control 3 months later) would be recommended. In case of atypical hyperplasia, investigation and management as per usual clinical practice should be performed.

Given the recognised potential endometrial changes associated with ulipristal use, please discuss the proposed prescriber educational program to ensure target prescribers are aware of the need for periodic monitoring and appropriate follow up of women using ulipristal for the management of uterine fibroids.

2. Are there long term follow up efficacy and safety data for the 457 patients exposed to ulipristal acetate 5 mg or 10 mg for four 3 month courses (including bleeding profile, myoma size, endometrial safety)? Are there data available regarding the number of subjects who have undergone a surgical procedure?
3. The GnRH agonist leuprorelin is not registered in Australia for use in the management of uterine fibroids, although goserelin 3.6 mg is registered for this indication. The Clinical Expert stated in the Clinical Overview:

*the two GnRH agonists being similar, the active comparator selected in the study PGL07-022 and study findings are thus appropriate to conclude about the benefit of Esmya over medical therapies currently registered in Australia to manage uterine fibroids.*

Please provide further information to justify the statement “the two GnRH agonists being similar”.

4. Given Study PGL-W-001 was not considered conclusive regarding use in moderate hepatic impairment, are further studies planned to assess the use of ulipristal acetate in women with hepatic impairment?
5. Regarding Study PGL11-006, please provide regarding the frequency of treatment related AEs related to excessive uterine bleeding for subjects in Study PGL11-006 during and after ulipristal acetate treatment course 3 and treatment course 4.

## **Second round evaluation**

Details of sponsor’s responses to clinical questions and evaluator’s subsequent comments are contained in Attachment 2.

## **Second round benefit-risk assessment**

### **Second round assessment of benefits**

After consideration of the responses to clinical questions, the benefits of ulipristal acetate in the proposed usage are unchanged from those identified in Round 1.

### **Second round assessment of risks**

After consideration of the responses to clinical questions, the risks of ulipristal acetate in the proposed usage are:

- Endometrial safety: further to comments above, while there are data from a small number of women exposed to 8 intermittent treatment courses, essentially long-term data on endometrial safety are lacking. A key consideration therefore is appropriate monitoring and follow up of patients using repeated intermittent ulipristal acetate treatment. The sponsor has provided the proposed education materials as part of the Section 31 response; adequacy of the prescriber and pathologist education material is

subject to expert clinical advice. A further issue for discussion is whether use of ulipristal acetate should be restricted to specialists pending availability of longer term endometrial safety data.

### Second round assessment of benefit-risk balance

The benefit-risk balance of ulipristal acetate 5 mg tablets, given the proposed usage, is uncertain due to the lack of long-term safety data.

### Second round recommendation regarding authorisation

Based on the data provided, there is no reason to reject the application to extend the indication for ulipristal acetate on efficacy grounds. However, given the lack of long term safety data, external expert clinical advice as to whether duration of treatment should be included in the proposed indication. 'Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age' is sought.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted an EU Risk Management Plan (RMP) Version 14.0 (dated 2 November 2015, DLP 31 July 2015) and Australian Specific Annex (ASA) (no version given) (dated December 2015) which was reviewed by the RMP evaluator.

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 8.

**Table 8: Ongoing safety concerns.**

Important identified risks	Inappropriate management of endometrium thickening (unnecessary interventions or treatments) Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)
Important potential risks	Acute uterine bleeding requiring immediate intervention Drug induced liver injury Treatment course beyond 3 months (this would be off-label use)
Missing information	Long-term effects of prolonged treatment of the endometrium (including possible malignant changes) Delayed diagnosis of hyperplasia with atypia or adenocarcinoma Impact on surgery Use in patients with moderate to severe hepatic impairment Use in patients with severe renal impairment

It is noted that the ulipristal acetate RMP for the indication of emergency contraception included the following safety concerns as shown in Table 9.

**Table 9. Safety concerns for ulipristal acetate RMP for the indication of emergency contraception.**

Important identified risks	None
Important potential risks	Effects on pregnancy maintenance/off-label use Risk of incomplete abortion and heavy bleeding Effects on foetus and newborns Risk of ectopic pregnancy Concomitant use of CYP3A4 inducers Liver effects Delayed menstrual period >60 days / amenorrhea Ovarian cysts
Missing information	Effect of concomitant use of progestin-only contraception Effect in patients with severe asthma treated by oral glucocorticoid Effects in women with impaired liver function

**RMP reviewer comment**

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification, the following recommendations are made:

The sponsor should add the following relevant safety concerns from the ulipristal acetate for emergency contraception) RMP:

- Concomitant use of CYP3A4 inducers
- Ovarian cysts
- Effects of interaction with progestin containing contraception

**Pharmacovigilance plan**

The sponsor proposes routine and additional pharmacovigilance activities (as stated above). The additional pharmacovigilance activities are summarised in Table 10.

**Table 10. Additional pharmacovigilance activities (planned or ongoing).**

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Prospective non-interventional study (PASS) PGL10-014: A prospective multicenter noninterventional study of women treated with Esmya (ulipristal	Inappropriate management of endometrium thickening (unnecessary interventions or treatments)  Inappropriate diagnosis of endometrial	Esmya use in "real world" practice	Final study report planned Q1 2016 (4 years post approval)

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
acetate) as pre-operative treatment of moderate to severe symptoms of uterine fibroids. (PREMYA, category 3)	<p>hyperplasia (mistaking PAEC for hyperplasia)</p> <p>Acute uterine bleeding requiring immediate intervention</p> <p>Drug Induced Liver Injury (DILI)</p> <p>Treatment beyond three months</p> <p>Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma</p> <p>Impact on surgery</p>		
Retrospective non interventional study (PASS) PGL11-020: Esmya prescription patterns in Europe: A retrospective drug utilisation chart review study. (PRECISE, category 3)	<p>Inappropriate management of endometrium thickening (unnecessary interventions or treatments)</p> <p>Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)</p> <p>Treatment beyond three months</p> <p>Impact on surgery</p>	Esmya use in "real world" practice	Final study report planned Q4 2015
Prospective, noninterventional study (PASS) PGL14-001: A prospective, noninterventional study to evaluate the long term safety of Esmya, in particular the	<p>Inappropriate management of endometrium thickening (unnecessary interventions or treatments)</p> <p>Inappropriate diagnosis of endometrial</p>	Esmya use in "real world" practice	Final report planned in Q1 2023 (8 years after variation approval)



Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
endometrial safety, and the current prescription and management patterns of Esmya in a long term treatment setting. (PREMIUM, category 3)	hyperplasia (mistaking PAEC for hyperplasia)  Acute uterine bleeding requiring immediate intervention  Drug Induced Liver Injury (DILI)  Treatment beyond three months  Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma  Impact on surgery		
Clinical trial PGL11-024: A Phase III, extension study of repeated intermittent 3-month courses of open-label of 10 mg ulipristal acetate. (PEARL extension 2, category 3)	Long-term effects of prolonged treatment on the endometrium	Safety and efficacy in total eight 3-month treatment courses	Final report in Q3 2015

**RMP reviewer comment**

The existing, ongoing and planned pharmacovigilance activities are considered acceptable for the purposes of this submission.

The sponsor should make the result of PEARL study (PGL11-024) available to TGA.

**Risk minimisation activities****Sponsor's conclusion in regard to the need for risk minimisation activities**

The sponsor is proposing additional risk minimisation activities.

**RMP reviewer comment**

The sponsor's conclusion is acceptable.

**Reconciliation of issues outlined in the RMP report**

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

***Recommendation #1 in RMP evaluation report***

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

***Sponsor response***

This is agreed.

***Evaluator's comment***

The sponsor's response has been noted.

***Recommendation #2 in RMP evaluation report***

The ASA should contain a version number.

***Sponsor response***

The applicant agrees with the recommendation. A revised RMP is provided.

***Evaluator's comment***

The sponsor's response has been noted. However, the currently provided ASA does not have a version number. This should be provided.

***Recommendation #3 in RMP evaluation report***

The sponsor should add the following relevant safety concerns from the ulipristal acetate for emergency contraception) RMP:

- Concomitant use of CYP3A4 inducers
- Ovarian cysts
- Effects of interaction with progestin containing contraception

***Sponsor response***

Although EllaOne for emergency contraception (30 mg UPA tablets single dose) and Esmya for uterine fibroid treatment (5 mg ulipristal acetate tablets, continuous daily dose for intermittent 3 months courses) contain the same active principle molecule, there are several differences between the 2 products which are considered critical regarding safety concerns.

- The indications of the 2 products and the context of drug provision are totally different.
- The tablet dosage and mode of administration are different, making the associated safety concerns potentially totally different. This is particularly important for the risk of potential interactions with any other medication.

In the case of EllaOne, the risk of unwanted pregnancy exists at the time of dosing, and the possible lack of efficacy in the form of the occurrence of a pregnancy is clearly identified (all or nothing risk), and can truly be considered as a safety concern. The medication should be administered immediately at the time of prescription, with any delay increasing

the risk of unwanted pregnancy. This context makes it difficult to manage potential concomitant uses and the risk of pregnancy, which is already present at the time of prescription, becomes prominent versus the risk of a potential interaction.

Regarding Esmya, there is time to weigh the benefits and risks of any concomitant treatment, time to interrupt any other chronic treatment if Esmya treatment is considered by the prescribing physician as essential and beneficial for the patient. This benefit-risk assessment is routine practice when a new chronic treatment is introduced.

For all these reasons, the applicant considers that the list of potential risks associated to Esmya use should be evaluated anew and not be derived solely from the elements included in the EllaOne dossier.

***Evaluator's comment***

This is considered acceptable in the context of this application, but may be reviewed in future submissions.

***Recommendation #4 in RMP evaluation report***

The sponsor should make the result of PEARL study (PGL11-024) available to TGA.

***Sponsor response***

The clinical study report of PGL11-024 is provided. Results are described in the revised versions.

***Evaluator's comment***

The sponsor's response has been noted.

***Recommendation #5 in RMP evaluation report***

The sponsor should commit to the same additional risk minimisation activities in Australia as conducted in the EU, in the form of educational material to prescribers and pathologists.

***Sponsor response***

As it was done in EU, the sponsor commits to implement additional risk minimisation activities in Australia, in the form of educational material to prescribers and pathologists. Details are provided in the Response Document.

***Evaluator's comment***

The sponsor's response has been noted.

***Recommendation #6 in RMP evaluation report***

Prior to approval, the sponsor should provide TGA with the education materials proposed for the Australian market.

***Sponsor response***

The sponsor proposes to use similar educational materials in Australia than those that are used and have been tested in EU (most recent submitted versions are provided in Appendix to the RMP).

***Evaluator's comment***

The sponsor's response has been noted.

The materials are currently being reviewed by a pathologist. The sponsor will be notified if changes need to be made.

## Summary of recommendations

It is considered that the sponsor's response to the TGA Section 31 Request has adequately addressed most the issues identified in the RMP evaluation report.

### **Outstanding issues**

*Issues in relation to the RMP*

- The ASA should contain a version number.
- The education materials are currently being reviewed by a pathologist. The sponsor will be notified if changes need to be made.

### **Comments on the safety specification of the RMP**

*Clinical evaluation report*

The clinical evaluator made the following second round comment in regard to safety specifications in the draft RMP:

*The Safety Specification in the draft Risk Management Plan is satisfactory.*

*Regarding long term endometrial safety, the sponsor proposes the following routine and additional pharmacovigilance activities to address the missing information with respect to long term effects of prolonged treatment on the endometrium (including possible malignant changes) and delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma:*

- *Routine pharmacovigilance practices*
- *Review in PSURs*
- *Non-interventional study PGL14-001: Study protocol Version 1.2 provided.*

*Study PGL14-001 (PREMIUM) is a prospective, multinational, multicentre, non-interventional post authorisation safety study to assess the long term safety of Esmya, in particular endometrial safety, and the current prescription and management patterns of Esmya in a long term treatment setting.*

*The specific study objectives are:*

- *Assess the long term safety, including endometrial safety, of Esmya in standard medical practice.*
- *Assess prescription patterns of Esmya in standard medical practice in long-term treatment setting.*

*The target population is women with moderate to severe symptoms of uterine fibroids for whom treatment with Esmya in a long-term manner is planned. Further, subjects who were previously exposed to ulipristal acetate 5 mg or 10 mg in the long term Phase III trials (PGL11-006 and PGL09-027 including extension PGL11-024) will be contacted and followed up. Those patients prescribed Esmya for pre-operative treatment are excluded from this study.*

*The planned enrolment is approximately 1500 eligible patients from 100-150 clinical practice sites in the EU. Patients will be followed for an observation period of 60 months from treatment start, with Investigators to manage patients as per their standard medical practice. Study visits will occur at enrolment and then according to the standard practice of the physician; this is assumed to include visits approximately every 8 months (after two treatment courses) at a minimum. There are no specific diagnostic tests or treatments after Esmya initiation required for this study.*

*The following endpoints will be assessed:*

- *collect/follow symptoms related to long term safety, including endometrial safety:*
  - i. *evaluate symptoms related to endometrial safety (for example, abnormal bleeding patterns) and treatment/interventions performed.*
  - ii. *frequency of findings of endometrial thickening >16 mm and document follow-up investigations/treatments/interventions performed.*
  - iii. *frequency of diagnosis of endometrial hyperplasia and follow-up investigations/treatments/interventions performed and rate at which diagnosis confirmed by second opinion.*
  - iv. *evaluate any reports of endometrial adenocarcinoma and outcome.*
  - v. *all SAEs, gynaecological AEs, AEs leading to treatment discontinuation, all pregnancies.*
- *collect prescription patterns of Esmya and clarify extent of long-term exposure (number of treatment courses, duration of treatment with Esmya during each treatment course), demographics of patients treated with Esmya.*
  - vi. *Sub-group analyses will include: all patients completing at least 4 treatment courses within the study period, all patients with any individual treatment course > 3 months, and all patients previously treated in the long-term Phase III studies.*
  - vii. *Progress reports will be undertaken on a yearly basis with a final study report generated at the end of the study.*

#### *Nonclinical evaluation report*

The nonclinical evaluator made the following comment in regard to safety specifications in the draft RMP:

*Results and conclusions drawn from the nonclinical program for ulipristal acetate (ESMYA) detailed in the sponsor's draft Risk Management Plan are mostly in general concordance with those of the Nonclinical Evaluator.*

*Additional findings that should also be listed as a potential risk based on nonclinical findings of unknown significance are the endometrial changes (cystic dilatation, squamous metaplasia, cystic endometrial hyperplasia) observed in two long term (6 and 9 month) monkey studies. Endometrial hyperplasia results when levels of oestrogen are high but progestins are low, and is a risk factor for endometrial cancer. A number of HRT oestradiol only products on the ARTG (for example, Estraderm patches, Estrofem tablets) contain precautionary statements in their PIs advising against prolonged use of unopposed oestrogen products, albeit for products intended to be used 5 years and more. The relevance of this to Esmya is that, although a single treatment course is 3 months, the proposed PI refers to long term treatment of up to 4 intermittent treatment courses, and no maximum number of courses allowed is identified. Therefore, animal endometrial findings should be highlighted in the RMP if the treatment duration extends beyond a single 3 month treatment course.*

#### **RMP reviewer comment**

It is noted that long term effects of prolonged treatment on the endometrium is already contained in the safety specification.

#### **Key changes to the updated RMP**

EU RMP Version 13.2 (dated 19 March 2015, DLP 22 February 2015) and ASA (dated April 2015) has been superseded by:

- EU RMP Version 14.0 (dated 2 November 2015, DLP 31 July 2015) and ASA (no version given) (dated December 2015).

**Table 11. Summary of key changes between EU-RMP Version 13.2 and EU-RMP Version 14.0.**

Summary of key changes	
Safety specification	No changes to safety concerns/missing information. Updates with results of PREPAR and PRECISE studies.
Pharmacovigilance activities	Updates with results of PREPAR and PRECISE studies.
Risk minimisation activities	No changes
ASA	Updates to reflect changes to the EU-RMP and changes to the PI document.

### ***Suggested wording for conditions of registration***

#### *RMP*

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

*Implement EU RMP Version 14.0 (dated 2 November 2015, DLP 31 July 2015) and attached ASA (dated December 2015), and any future updates, where TGA approved, as a condition of registration.*

*[If the proposed final additional materials are not received before approval, additional wording with regard to the materials should be inserted:*

*Provide and implement Additional Risk Minimisation Activities, within 3 months of approval, where approved by the TGA Pharmacovigilance and Special Access Branch (PSAB), as a condition of registration.]*

## **VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations:

### **Quality**

The pharmaceutical chemistry evaluator did not have any objections to registration (besides one GMP issue, which was resolved).

### **Nonclinical**

There were no nonclinical objections to the registration of Esmya.

Embryofoetal lethality of ulipristal has been shown in multiple laboratory animal species at low or subclinical exposure levels. The sponsor proposes contraindication in pregnancy

and assignment to Pregnancy Category D, which was supported by the nonclinical evaluator.

Chronic administration of ulipristal produced histopathological changes in the endometrium of monkeys, comprising endometrial thickening, cystic endometrial hyperplasia, squamous metaplasia and cystic dilatation. This occurred at all dose levels tested, and the changes were reversible when ulipristal treatment was withdrawn.

Ulipristal was shown not to be carcinogenic in studies in rats and transgenic mice.

## Clinical

### Pharmacodynamics & Pharmacokinetics

Most of the PK and PD studies were previously evaluated as part of the EllaOne submission. An additional study (PGL-W-001) was submitted that compared PK in 8 women with moderately impaired hepatic function versus 8 healthy women. However, there was overlap in PK parameters between women in the two groups, so that the results were not materially informative. The proposed PI recommends: mild hepatic impairment – no dosage adjustment; moderate/severe hepatic impairment – not recommended, unless the patient is closely monitored.

### Efficacy

The available Phase III studies on efficacy (and safety) were:

- *To support use for up to 3 months before surgery (largely as an alternative to pre-operative use of GnRh agonist)*

Three studies of one course (of 3 months duration)

- PGL07-021 (PEARL I)<sup>22</sup>
- PGL07-022 (PEARL II)<sup>23</sup>
- PGL09-026 (first cycle of PGL09-027) [see below]

- *To support use as a long term alternative to surgery*

Two studies of four intermittent courses (each course was 3 months duration):

- PGL09-027 (PEARL III; 10 mg; first course was PGL09-026)<sup>24</sup>
- PGL11-006 (PEARL IV; 5 and 10 mg)<sup>25</sup>
- In the MS4 response, the sponsor submitted the results of PGL11-024 (an extension of PGL09-026 [1 course] and PGL09-027 [a further 3 courses]) (PEARL III) for a further 4 courses; giving 8 courses in total, with the 10 mg dose. 64 women started treatment; 53 (83%) completed; 43 had biopsy results.

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<sup>22</sup> Donnez J, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med.* 366: 409-420 (2012).

<sup>23</sup> Donnez J, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med.* 366: 421-432 (2012).

<sup>24</sup> Donnez J, et al. Long-term treatment of uterine fibroids with ulipristal acetate. *Fertil Steril.* 101: 1565-73.e1-18 (2014).

<sup>25</sup> Donnez J, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. *Fertil Steril.* 103: 519-27.e3 (2015).

***Evidence of efficacy for a single 3 month course before surgery***

Ulipristal (5 mg tablet) was registered for one 3 month pre-operative course in the EU in 2012 and Canada in 2013; there are various published summaries of this evidence; see for example, Canadian Agency for Drugs and Technology in Health. Ulipristal (5 mg tablets). Treatment of Moderate to Severe Signs and Symptoms of Uterine Fibroids in Adult Women of Reproductive Age Who are Eligible for Surgery, Ottawa, 2013.

Briefly, these studies recruited pre-menopausal women (just over 40 years of age, on average) who had characteristics similar to those women who might use the product should it be registered in Australia. They were perhaps thinner than some women with fibroids (mean BMI: 25 kg/m<sup>2</sup>) and the fibroids were of moderate, rather than large, size (inclusion criteria: myomatous uterus ≤16 weeks pregnancy; at least one fibroid ≥3 cm and none >10 cm).

Ulipristal was superior to placebo and noninferior to leuprorelin for the control of bleeding. More than 90% of women treated with either the 5 mg or 10 mg daily dose of ulipristal had a clinically significant decrease in bleeding and about three-quarters became amenorrhic. Ulipristal led to amenorrhea faster than leuprorelin and resulted in a greater increase in haemoglobin levels than placebo; although iron supplementation alone has been shown to be an effective for the pre-operative management of anaemia.<sup>26</sup> leuprorelin may be more effective in reducing fibroid bulk than ulipristal; regrowth after ceasing treatment may be faster with leuprolide.

***Evidence of efficacy to support repeated intermittent long-term use***

The inclusion/exclusion criteria for these multiple course studies were largely in line with those of the single course studies, except that women in these multiple course studies were not required to be eligible for surgery. The baseline characteristics were similar: age just over 40 years, BMI~25 kg/m<sup>2</sup>, fibroids of moderate size (<16 weeks), moderate/severe symptoms.

No placebo arm was included; although PGL-006 included a comparison to 10 mg. A placebo arm was considered unethical in women with heavy menstrual bleeding (that is, these women were not considered suitable for watchful waiting). There is no medicine that could serve as an active comparator for long term use. Surgery (including procedures less radical than hysterectomy) is a possible comparator for those women willing to consider surgery (see “Summary of safety concerns, missing information” under RMP).

Ulipristal was started during the first 4 days of menstruation. Courses were separated by an off treatment interval. Subsequent courses were commenced on the second off-treatment menstruation. That is, the off treatment interval included one complete menstrual bleed and the beginning of a second bleed.

The data showed that about 70% of women on the 5 mg dose had control of bleeding (no episodes of heavy bleeding and a maximum of 8 days bleeding over 56 days) after four treatment courses. There were reductions in fibroid and uterine volume and clinically relevant effects on pain and quality-of-life. Overall 60-80% of women were satisfied with treatment, based on the Global Study Treatment Satisfaction Questionnaire (GSTSQ). The GSTSQ was the primary endpoint for the extension study PGL11-024 (that is, the study comprising 64 women who completed Study PGL09-027. The UFS-QoL was the QoL secondary endpoint in the two long term studies.

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<sup>26</sup> Stovall TG, et al. GnRH agonist and iron versus placebo and iron in the anemic patient before surgery for leiomyomas: a randomized controlled trial. Leuprolide Acetate Study Group. *Obstet Gynecol.* 86: 65-71 (1995).



The GSTSQ consists of 4 questions:

- How satisfied or dissatisfied are you with the ability of the study drug to prevent or treat your fibroid symptoms?
- How satisfied or dissatisfied are you with the way the study drug relieves the uterine bleeding?
- Taking all things into account how satisfied or dissatisfied are you with this study drug?
- How do you estimate your menstrual bleeding now compared to before the very first intake of this study drug?

There were only minor differences in efficacy (and safety) between the 5 mg daily dose and the 10 mg daily dose. The 5 mg dose is the dose proposed for registration.

### ***Surgery***

In the pivotal study PGL11-006, there was a difference in the primary efficacy endpoint (percentage of subjects in amenorrhoea) for the 5 mg versus 10 mg dose, however when taking in to consideration other bleeding endpoints, the results were generally similar between the two groups.

Study PGL11-006; during the study there were 16 (3.5%) of subjects who underwent surgery; n = 4 (treatment course 1), n = 6 (treatment course 2), n = 2 (treatment course 3), n = 4 (treatment course 4).

There were no long term follow up data available for the 457 patients exposed to ulipristal acetate 5 mg or 10 mg for four 3 month courses, other than for the 64 patients from Study PGL09-027 who continued in to the extension Study PGL11-024 (further four intermittent 3 month courses of UPA 10 mg). During this study, 4 (6.3%) subjects underwent surgery (n = 1 treatment course 5, n = 1 treatment course 6, n = 2 treatment course 7).

### ***Safety***

In the pre-market studies, 1053 women were exposed to ulipristal for at least 3 months at doses of 5 mg or higher. Of these, 541 women were exposed to 2 or more courses and 446 women were exposed to 4 or more treatment courses. In PGL11-024, 53 women were exposed to 8 x 3 month courses at the 10 mg dose. Of these, 43 women had biopsy results available.

Based on the available data, 5 mg ulipristal is generally well tolerated; the most common adverse events, reported from the pre-market studies, were headache and hot flushes, most of which were of mild to moderate intensity. Also, in the pre-market studies, adverse events were more common for the first treatment course than for subsequent treatment courses.

In the study of pre-operative, short term (single course) use that directly compared ulipristal to leuprolide (head-to-head), ulipristal appeared to have a more favourable adverse effects profile, with less profound suppression of oestradiol levels, fewer hot flushes, and no major effects on markers of bone turnover.

### ***Endometrial safety***

Endometrial safety data were obtained from ultrasound (endometrial thickness) and biopsies (hyperplasia/carcinoma and non-physiological changes).

The occurrence of hyperplasia with ulipristal in the pre-market clinical development program was <1% (similar to published data for pre-menopausal women generally). There is no evidence, from the pre-market data, that up to four repeated intermittent courses increases the risk of more serious conditions of the endometrium such as

hyperplasia with atypia or endometrial carcinoma. Although an important caveat is that, given the current length of follow-up, a lagged effect leading to an increased future latent risk has not been excluded.

Multiple intermittent 3-month courses of ulipristal did not increase the occurrence of PAECs compared to a single course. Based on the available evidence, at this point in time, PAECs do not seem to increase the risk of more serious conditions of the endometrium such as hyperplasia with atypia or endometrial carcinoma. Although the sample size was small (n = 43), PGL11-024 suggested that exposure to 8 intermittent treatment courses (at the 10 mg dose) did not increase the occurrence of PAEC, compared with fewer courses.

Due to the mechanism of action of ulipristal, reversible thickening of the endometrium is expected. The incidence of thickened endometrium (>16 mm) increased from 1-5% (baseline) to 9-14% after one treatment course. The proportion of women with thickened endometrium with return of menstruation at the end of the 3-month treatment cycle was similar to baseline proportions. PGL11-024 showed that endometrial thickening did not increase with repeated cycles (although sample size was small).

If the endometrial thickening persists after return of menstruation during off treatment periods or beyond 3 months following the end of the treatment courses, it may need to be investigated, as per standard clinical practice, to exclude other conditions. This is in the Precautions section of the proposed PI (which the sponsor has taken from the EMA Summary of Product Characteristics (SmPC)). For women having repeated intermittent treatment, periodic monitoring of the endometrium (for example, annual US preferably after resumption of menstruation during an off treatment period) is recommended in the proposed PI (as in the EMA SmPC).

### ***Breast cancer***

The pre market data did not raise any concerns about breast cancer. Based on current knowledge, selective PRMs are not associated with an increased risk of breast cancer.

### ***Post market data***

The sponsor submitted five PSUR documents. These were all for the single pre-operative course. The post market exposure was estimated at 107,500 women. No new safety concerns were identified and no regulatory action was taken.

## **Risk management plan**

### **Summary of safety concerns**

These are listed below in Table 12.

**Table 12. Safety concerns.**

Important identified risks	Inappropriate management of endometrium thickening (unnecessary interventions or treatments) Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)
Important potential risks	Acute uterine bleeding requiring immediate intervention Drug induced liver injury Treatment course beyond 3 months (this would be off-label use)
Missing information	Long term effects of prolonged treatment of the endometrium (including possible malignant changes) Delayed diagnosis of hyperplasia with atypia or adenocarcinoma Impact on surgery Use in patients with moderate to severe hepatic impairment Use in patients with severe renal impairment

**Risk mitigation strategies*****Important identified risks***

- Inappropriate management of endometrium thickening (unnecessary interventions or treatments)

What is known:

- Because the thickening of the endometrium observed under ulipristal treatment has been shown to wane during the off-treatment interval and does not indicate an underlying condition, this risk is limited to triggering unnecessary investigations (for example, endometrium biopsy, hysteroscopy, dilation and curettage) or treatment (that is, a progestagen for a few weeks). These unnecessary investigations or treatment carry some risks for the women and would be inconvenient (and could be expensive, although TGA does not consider cost).

Prevention:

- The incidence of endometrium thickening in patients treated by SPRM cannot be prevented. It wanes spontaneously after the first spontaneous menstruation, which follows treatment completion, with a complete reversibility demonstrated at one month. To prevent the risk of inappropriate management of this transient endometrium thickening, prescriber education is planned; similar to that in the EU.
- Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)  
As above + pathologist education.

***Important potential risks***

- Acute uterine bleeding requiring immediate attention

This relates to another SPRM (telapristone, Proellex). Continuous treatment for more than five months induced acute uterine bleeding in a few subjects who had shown increase in endometrial thickness in response to the treatment. The sponsor says that there are no similar reports from either the pre-market data or post-market data for ulitpristal and makes the point that the condition being treated (fibroids) is associated with heavy bleeding.

- Drug Induced Liver Injury (DILI)

Clinically relevant elevations in liver enzymes have been noted in studies with telapristone and onapristone, but not with other SPRMs including ulipristal, asoprisnil or mifepristone, suggesting that this may not be a class effect. The sponsor notes that no cases of DILI nor any effect on liver function tests (suggesting liver injury) were reported during pre-market clinical development program or post market.

- Off label treatment duration

There is the potential for continuous use of ulipristal for longer than 3 months in women who get symptomatic relief (less bloating and discomfort due to reduced fibroid size, increased energy due to less heavy bleeding). This type of use poses a risk because intermittent use induces a type of withdrawal bleed, which would offset any developing endometrial hyperplasia. That is, intermittent courses allow menstrual shedding of the endometrium and allow a complete menstrual cycle to take place between each treatment course, with physiological progesterone influence on the endometrium. This risk will be mitigated by statements in the PI and prescriber education.

### ***Missing information***

- Long term effects of prolonged treatment of the endometrium (including possible malignant changes)

This is the major weakness in the available data. There could be a latency period, in which case the lagged effect of ulipristal would not have been detected yet.

- Delayed diagnosis of atypical endometrial hyperplasia or adenocarcinoma

Mitigated to some extent by statements in the PI and prescriber education.

- Impact on surgery

Unknown

- Use in patients with moderate to severe hepatic impairment and patients with severe renal impairment.

The risks posed by this missing data will be mitigated by statements in the PI. (Ulipristal is mainly metabolised by the liver.)

### ***Additional pharmacovigilance activities***

Besides spontaneous adverse event reporting, the following additional pharmacovigilance activities are planned in the EU. (These studies do/will not involve any Australian patients because recruitment is complete or nearly complete for most of these studies.) The studies have been endorsed by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC).

#### ***PGL10-014; PREMYA***

- This non-randomised study without a control group is following up women with moderate to severe symptoms of uterine fibroids for 15 months after they have started a pre-operative single treatment of ulipristal 5 mg for 3 months.
- Sample size: 1534 enrolled; 228 (14%) discontinued.
- 133 sites; 10 EU countries.
- Recruitment began in May 2012 and finished in Apr 2014.
- Data collection finished in Q3 2015.

- Annual reports were submitted to the EMA in 2013, 2014, 2015 and these were also submitted to TGA during the evaluation. The final report is under preparation and is due Q1 2016.
- Preliminary results showed that about one-third of women had a surgical procedure following the single course of ulipristal.
- The sponsor reports that no new safety concerns were identified.

#### *PREPAR*

- A survey of the effectiveness of the education program for potential prescribers
- Results were submitted to EMA in March 2015 and also provided to TGA. The proportions responding were low (gynaecologists: 5%; pathologists: 2%)
- In the s.31 response, the sponsor submitted the results of PGL11-024 (an extension of PGL09-026 [1 course] and PGL09-027 [a further 3 courses]) (PEARL III) for a further 4 courses; giving 8 courses in total. Sample size was 50-60 women. This was largely a safety study.

#### *PGL14-001 (PREMIUM)*

- To assess the long term safety (especially endometrial safety) of long-term, repeated use of Esmya
- Prospective, multi-centre, non-interventional PASS to assess long term safety, particularly endometrial safety, in long term treatment setting.
- Target population is women with moderate to severe symptoms of uterine fibroids for whom treatment with Esmya in a long-term manner is planned. Subjects previously exposed to ulipristal acetate 5 mg or 10 mg in the long-term Phase III trials (PGL11-006 and PGL09-027 including extension PGL11-024) will be contacted and followed up. Those patients prescribed Esmya for pre-operative treatment are excluded.
- Planned enrolment is approximately 1500 eligible patients from 100-150 clinical practice sites in the EU.
- Patients will be followed for an observation period of 60 months from treatment start, with Investigators to manage patients as per their standard medical practice.
- End-points to be assessed include: symptoms related to endometrial safety, frequency of endometrial thickening >16 mm and endometrial hyperplasia and follow up investigations/management, any reports of endometrial cancer.
- Yearly progress study reports.

#### ***Additional risk minimisation measures***

From the sponsor's ASA:

*In the EU, educational materials for prescribers (gynaecologists) and pathologists were distributed at the time of initial launch (for pre-operative, single-course use). It is proposed that the same kind of educational materials are distributed in Australia. The educational materials provide messages about:*

- *Inappropriate management of endometrium thickening (unnecessary interventions or treatments)*
- *Inappropriate diagnosis of endometrial hyperplasia (mistaking PAEC for hyperplasia)*
- *Treatment course beyond 3 months*
- *Delayed diagnosis of hyperplasia with atypia or adenocarcinoma*

An attempt was made to evaluate this educational intervention (additional risk minimisation measure) via the PREPAR survey. As outlined above, response rates were low (< 5%).

## **Risk-benefit analysis**

### **Delegate's considerations**

Studies have shown that ulipristal 5 mg results in control of bleeding for about 70% of women, which was maintained for 4 intermittent treatment courses. Reductions in myoma and uterine volume were observed and there were clinically relevant effects on pain and quality-of-life. Greater than 50% of women were satisfied with treatment with ulipristal. Consequently, at this point in time, pending further advice, efficacy is satisfactorily established for the proposed usage (intermittent treatment of moderate to severe symptoms of uterine fibroids; which could include pre-operative treatment, should the woman subsequently choose surgery.).

Currently, adequate, pre market data for safety are available for up to four intermittent treatment cycles. PGL11-024 (43 endometrial biopsies) is too small to warrant reassuring statements in the PI (see Type II variation assessment report, December 2015).

The main weakness in the evidence base is lack of long term data. This will be mitigated by statements in the PI. Post-marketing studies are planned or underway to better characterise long-term endometrial safety.

Given the effectiveness and safety-profile of surgery for fibroids in Australia (including minimally invasive techniques and fertility-preserving procedures), the clinical place of repeated, intermittent use of a medicine, such as ulipristal, is unclear. It is possible that, some women – after a full discussion of the benefits and risks of ulipristal (especially the limitations of the data on long-term safety) – might decide that they prefer not to have surgery. However, management of moderate/severe symptoms of fibroids should involve interaction with secondary care (that is, not exclusively in the primary care setting); and should involve gynaecologists, who can offer surgery as a management option.

### ***Conditions of registration***

- Standard conditions will apply about implementing the RMP, which includes a listing of post marketing studies.

### ***Pathologist's guide to ulipristal-associated endometrial changes***

The TGA sought independent expert advice from an Australian pathologist, who is an expert in endometrial histology. The advice will be provided to the sponsor and the ACPM.

## **Proposed action**

The main weakness in the evidence base is lack of long-term data on safety. This will be mitigated by statements in the PI. Post marketing studies are planned or underway to better characterise long term endometrial safety.

The Delegate has no reason to say, at this time, that Esmya should not be approved for registration.

## **Request for ACPM advice**

The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

**Response from sponsor**

The sponsor has the following comments on the Request for ACPM's Advice for the application to register the Esmya product in Australia.

- *The Delegate notes in Pharmaceutical Chemistry of the Request for ACPM's Advice that one GMP issue "was expected to be resolved".*

The sponsor confirms the GMP clearance issue is resolved.

**Advisory committee considerations**

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Esmya tablet containing 5 mg of ulipristal acetate to have an overall positive benefit-risk profile for the indication;

*Esmya is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.*

In making this recommendation, the ACPM:

- noted efficacy has been demonstrated to be predictable and clinically meaningful
- noted the safety profile from submitted data are reassuring; however, the data are too short term and from insufficient patient numbers to deliver certainty about long term use or latent toxicity
- noted several pharmacovigilance studies are planned or underway in the EU, including a 5 year endometrial safety study

**Proposed conditions of registration**

The ACPM agreed with the Delegate on the proposed conditions of registration. The ACPM agreed with the RMP inclusions of education strategies for gynaecologists and pathologists on endometrial changes with SPRM use and on the potential dangers of continuous use.

**Proposed PI/CMI amendments**

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI, particularly the inclusion of statements regarding;

- the implications of the lack of long term uterine safety data
- the lack of data on use in hepatic and renal impairment.

The ACPM advised that the benefit-risk balance is considered positive, with long term safety concerns sufficiently qualified by the RMP and PI statements.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

**Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Esmya ulipristal acetate 5 mg tablet blister pack indicated for:

*Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.*

### **Specific conditions of registration applying to these goods**

- The Esmya (ulipristal acetate) EU RMP, Version 14.0, dated 2 November 2015 (DLP 31 July 2015) and attached ASA Version 02, dated December 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## **Attachment 1. Product Information**

The PI approved for Esmya at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## **Attachment 2. Extract from the Clinical Evaluation Report**



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