Medicines Adverse Reactions Committee

Meeting date	**3 July 2018**	Agenda item	3.1.1
Title	**Consideration of Esmya (ulipristal acetate) under section 36 of the Medicines Act 1981**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent	**Medicines**	**Sponsors**	
Ulipristal acetate	Esmya 5 mg tablets	Pharmacy Retailing (NZ) Ltd trading as Healthcare Logistics	
Funding	Not funded		
Previous MARC meetings	Esmya (ulipristal acetate) has been discussed previously at the following meeting: – 173rd Meeting — 8 March 2018 Ulipristal acetate and drug induced liver injury		
International action	EMA [1] – 1 June 2018: The EMA completed their review and recommended that several measures be put in place to minimise the risk of rare but serious liver injury with Esmya (ulipristal acetate).		
Schedule	Prescription medicine		
Usage data	Two patients have been treated with Esmya (ulipristal acetate) in New Zealand		
Advice sought	**The Committee is asked to advise whether:** – The balance of benefits and risk for the use of Esmya (ulipristal acetate) for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age is favourable. – Any regulatory action is required (eg, that the recommendations from the PRAC are also implemented in New Zealand) to improve the balance of benefits and risks.		

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1.0 PURPOSE

At the previous meeting the Committee reviewed the available information on the possible risk of drug induced liver injury with Esmya (ulipristal acetate) (the report is attached at Annexe 1). The Committee recommended that Medsafe conduct a benefit risk review of Esmya (ulipristal acetate) 5 mg under section 36 of the Medicines Act 1981.

The purpose of this paper is to review the information provided by the company in response to the section 36 notice.

2.0 BACKGROUND

2.1 Esmya (ulipristal acetate)

The active substance in Esmya, ulipristal acetate, is a synthetic derivative of progesterone (see comparison of structures in Figure 1) [2]. It is an orally active selective progesterone receptor modulator that acts via high affinity binding to the human progesterone receptor.

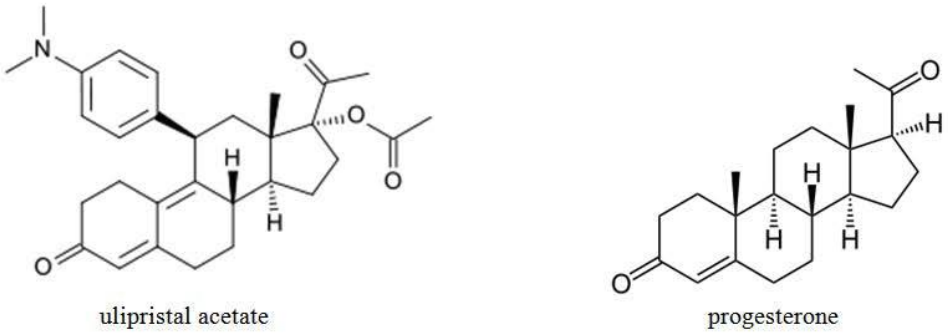

Figure 1: Chemical structures of ulipristal acetate and progesterone

Ulipristal acetate works by attaching to the targets on cells (receptors) that the hormone progesterone normally attaches to, preventing progesterone from having its effect.

Ulipristal acetate exerts a direct effect on the endometrium and a direct action on fibroids reducing their size through inhibition of cell proliferation and induction of apoptosis.

Esmya was first authorised in the European Union in 2012 for the treatment of moderate to severe symptoms of uterine fibroids (ie, non-cancerous (benign) tumours of the womb) in women who have not reached menopause [1]. It is used for up to three months before women undergo surgery to remove the fibroids. The three-month course can be repeated with breaks between each course.

Esmya was approved in New Zealand on 7 December 2017 for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age [3]. Repeated intermittent treatment has been studied up to four intermittent courses.

In some countries, ulipristal acetate is also indicated for emergency contraception [2]. ellaOne was approved in the European Union in 2009 for emergency contraception within 120 hours (five days) of unprotected sexual intercourse or contraceptive failure.

There are no ulipristal acetate containing products approved in New Zealand that are indicated for emergency contraception.

Comments:

Esmya (ulipristal acetate) was approved in New Zealand on 7 December 2017 and to date only two patients have been treated. To prevent an unlikely event of a new patient commencing therapy, a temporary hiatus of sales by the distributor has been implemented.

2.2 Summary of the EMA review

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the benefits and risks with Esmya (ulipristal acetate), following reports of serious liver injury, including liver failure leading to transplantation [1].

At its meeting on 14-17 May 2018, the PRAC concluded that Esmya (ulipristal acetate) may have contributed to the development of some cases of serious liver injury. In eight cases of serious liver injury, a role of Esmya (ulipristal acetate) in contributing to these cases is possible. The PRAC has therefore made the following recommendations to minimise this risk:

- Esmya (ulipristal acetate) must not be used in women with known liver problems.
- A liver function test should be performed before starting each treatment course and treatment must not be started if liver enzyme levels are more than two times the upper limit of normal.
- Liver function tests should be performed once a month during the first two treatment courses and two to four weeks after stopping treatment. If the test is abnormal (liver enzyme levels more than three times the upper limit of normal), the doctor should stop treatment and closely monitor the patient.
- Esmya (ulipristal acetate) should be used for more than one treatment course only in women who are not eligible for surgery. Women who are about to have surgery should continue to use only one course.
- A card will be included in the box of the medicine to inform patients about the need for liver monitoring, and to contact their doctor should they develop symptoms of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting).
- Studies should be performed to determine the effects of Esmya (ulipristal acetate) on the liver and whether these measures are effectively minimising the risks.

In February 2018, while the review was ongoing, the PRAC had issued temporary recommendations that no new patients should be started on Esmya. Having finalised its review, the PRAC has now concluded that new patients can start treatment in line with the above recommendations to minimise the risk of liver injury.

The PRAC's recommendations have now been endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP) and will be sent to the European Commission for a final legal decision. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.

Comments:

The PRAC recommendations will only apply in Europe.

In Australia, the Therapeutic Goods Administration is awaiting the outcome of the EMA review before making a decision about any regulatory action.

2.3 Section 36 notice

On 22 March 2018, Medsafe issued the company a notice under section 36 of the Medicines Act 1981 (attached at Annexe 2).

The section 36 notice requested that the company provide the following information:

1. A summary of the efficacy of ulipristal acetate in the approved indication, including absolute numbers where available and data on comparators.
2. Details of any more reported cases of serious liver injury following the review already provided.
3. A copy of any additional information sent to the EMA's PRAC for their review.

4. Any further updates to the Risk Management Plan.
5. The latest Periodic Safety Update Report if it is available.
6. Any further analyses of the clinical trial data which may have been performed.
7. Proposals for any update to risk minimisation plans for New Zealand.

The company's response to the section 36 notice is presented in section 3.0 of this report.

Comments:

The New Zealand sponsor for Esmya (ulipristal acetate) is Pharmacy Retailing (NZ) Limited trading as Healthcare Logistics. The Australian sponsor is Vifor Pharma Pty Limited (Australia). Gedeon Richter is the marketing authorisation holder in Europe. For the purpose of this report, all three are referred to as 'the company'.

3.0 INFORMATION PROVIDED BY THE COMPANY

3.1 Response to the section 36 notice

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4.0 BENEFIT RISK REVIEW

4.1 Company benefit risk review

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4.2 Medsafe benefit risk review

4.2.1 Medsafe's pre-market clinical evaluation (attached at Annexe 6)

Medsafe's pre-market clinical evaluation included a discussion on efficacy, hepatic safety and a benefit risk assessment of Esmya (ulipristal acetate).

Efficacy

Table 2 below summarises the key design characteristics of the short-term and long-term efficacy studies.

Table 2: Efficacy study design characteristics for completed studies

Phase	Study	Design	Treatment Duration	Treatment groups	Dose	Number of subjects
III	PGL07-021 (PEARL I)	Double-blind, placebo controlled	12-13 weeks[a]	Ulipristal acetate[b]	5 mg/day	96
					10 mg/day	98
				Placebo[b]	-	48
	PGL07-022 (PEARL II)	Double-blind, double-dummy, active comparator controlled	12-13 weeks[a]	Ulipristal acetate	5 mg/day	102
					10 mg/day	103
				Leuprorelin	3.75 mg once a month[c]	102
	PGL09-026 (PEARL II)	Open Label for ulipristal acetate	90 days	Ulipristal acetate[d]	10 mg/day	209
	PGL09-027 (PEARL III extension)	Open Label for ulipristal acetate	additional 3 x 90 days[e]	Ulipristal acetate[d]	10 mg/day	132
	PGL11-024 (PEARL extension 2)	Open Label for Ulipristal acetate	Additional 4 x 90 days[e]	Ulipristal Acetate	10 mg/day	64
	PGL11-006 (PEARL IV)	Double-blind parallel group	4 x 84 days[e]	Ulipristal acetate	5 mg/day	228
					10 mg/day	223
II	PGL-N-0287	Double-blind, placebo controlled	12 weeks	Ulipristal acetate	10 mg/day	8
					20 mg/day	6
				Placebo	-	8
	PGL-N-0090	Double-blind, placebo controlled	12-24 weeks[f]	Ulipristal acetate	10 mg/day	14
					20 mg/day	14
				Placebo	-	13

a with a 6 months safety follow-up.

b 80 mg Fe^{2+} (Tardyferon®, containing 256.3mg of ferrous sulfate, equivalent to 80mg of Fe^{2+}) was administered daily, concomitantly in all treatment groups

c Administered as an intramuscular injection

d after 90 days of ulipristal acetate treatment, all subjects were randomized to receive a treatment of 10 days of 10 mg of NETA or placebo.

e treatment courses were separated by a drug free interval of approximately 6 weeks.

f Week 12 to Week 24 was an optional, unblinded extension period of ulipristal acetate treatment, which was undertaken by 4 subjects from the placebo group (2 each received ulipristal acetate 10 and 20 mg/day), 3 subjects in the ulipristal acetate 10 mg/day group and 6 subjects in the ulipristal acetate 20 mg/day group

In the short-term phase III studies, ulipristal acetate was found to be statistically significantly superior to placebo (study PGL07-021 [5]), and non-inferior to the gonadotropin-releasing hormone agonist, leuprorelin (study PGL07-022 [6]) for the primary/co-primary efficacy variable of the percentage of subjects with a reduction of uterine bleeding at the Week 13 Visit (defined as PBAC score <75).

In study PGL07-021 [5], the difference in the proportion of subjects with PBAC <75 between ulipristal acetate (>90%) and placebo (<20%) was very marked. Ulipristal acetate was also found to be statistically superior to placebo for the co-primary efficacy variable of change in total fibroid volume assessed by MRI from Screening to Week 13.

Study PGL11-006 [8] assessed the efficacy and safety of ulipristal acetate 5 mg versus 10 mg over a total of four intermittent 3-month treatment courses. This study was composed of two parts: part II included results in women treated with the first two 3-months treatment courses (up to visit 8) and part II included results after treatment courses 3 and 4 and the follow-up period.

In study PGL11-006 [8], the proportion of subjects in amenorrhoea at the end of each treatment course was similar in both the 5 mg/day group (71.8%, 74.1%, 73.3%, and 69.6% at the end of treatment courses 1 2, 3 and 4 respectively) and 10 mg/day group (82.6%, 82.2%, 78.3% and 74.5% at the end of treatment courses 1, 2, 3 and 4 respectively).

Amenorrhoea is a very demanding endpoint that considers subjects with few days of spotting as failures.

The improvements in bleeding results in study PGL11-006 [8] are considered clinically relevant.

There was a statistically significant difference in the 5mg and 10 mg treatment groups for the primary endpoints, amenorrhoea at the end of the first two courses, and at the end of all four treatment courses.

However, taking account of other bleeding parameters (number of subjects in amenorrhoea at the end of each treatment course, controlled bleeding), reduction in uterine and myoma volume, and improved quality of life indicators, the EMA and TGA have found the 5 mg dose having satisfactory efficacy.

The median PBAC in study PGL11-006 [8] was similar for the two dose groups.

In addition, no difference between the two doses was observed for all other efficacy endpoints (ie, fibroid volume reduction, pain reduction and Quality of Life improvement. Moreover both doses showed a good and comparable safety profile.

This resulted in the recommended dose for the new proposed indication of long-term (repeated intermittent) treatment being 5 mg/day.

Hepatic safety

One selective progesterone receptor modulator, onapristone, was discontinued from phase II trials as treatment for breast cancer because of hepatic safety concerns. Asoprisnil has also been discontinued from development for uncertain reasons. Concerns over liver safety have not been seen with other selective progesterone receptor modulators such as ulipristal acetate, asoprisnil and mifepristone, suggesting that this effect is most likely specific to telapristone acetate and onapristone and is not a class effect.

There was no evidence of liver toxicity based on the treatment emergent adverse events reported in the phase III studies (PGL07-021 [5], PGL07-022 [6], PGL09-026 [7] / PGL09-027 and PGL11-006 [8]), the phase II studies in the target population (PGL-N-0287 and PGL-N-0090) and the phase II study in healthy subjects (PGL-H-510).

In all the clinical trials of multiple dose administration of ulipristal acetate (including administration of 50 mg/day for 10 days in healthy volunteers in study PGL09-023) there have been only few cases of subjects having aspartate transaminase or alanine transaminase >3 x upper limit of normal range (ULN). In no case the increase of transaminases was associated with an increase in bilirubin and none of the above cases qualified for Hy's law.

In phase III studies, mildly elevated transaminase levels were reported for less than 5% of subjects from all treatment groups; the distribution of subjects with high values was similar across the three treatment groups. In general the elevations were less than 2 x ULN, were not associated with any increase in bilirubin and were transient.

Benefit risk assessment

Medical treatments of symptomatic fibroids are currently limited to short-term use prior to surgery and comprise either progesterone receptor modulators or gonadotropin releasing hormone agonists.

The benefit risk balance of the long-term, intermittent Esmya (ulipristal acetate) 5 mg tablet once daily for intermittent treatment courses (each up to three months duration) for the treatment of moderate to severe symptoms of uterine fibroids is positive.

This application was for the long-term, intermittent treatment of symptoms of uterine fibroids. Treatment courses are each of up to three months duration (one tablet of 5 mg to be taken once daily). Each course is to be separated by a drug-free interval until the start of the second menstruation from the end of the previous treatment course.

This application was supported by two key studies (with up to 8 and 4 treatment courses), PGL11-024 and PGL11-006 [8].

For study PGL11-024 (from courses 5th to 8th), the 64 subjects' satisfaction regarding the ability of study drug to control their myoma symptoms was high (as per Global Study Treatment Satisfaction Questionnaire - GSTSQ) and fibroid volume (measured by MRI) was reduced.

In study PGL11-006 [8], the proportion of subjects in amenorrhoea at the end of each treatment course was higher for those receiving 10 mg/day compared to those receiving 5 mg/day, although differences were not large. Other bleeding parameters (number of subjects in amenorrhoea at the end of each treatment course, controlled bleeding), reduction in uterine and myoma volume, and improved quality of life indicators, showed similar results for the 5 and 10 mg dose.

Overall UPA is generally well tolerated; the most common adverse events 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. (In addition, there is now post-marketing data for the 5 mg once daily tablet for uterine fibroids.)

In study PGL11-006 [8], the proportion of subjects with endometrial thickness >16 mm rose from 4.9% at screening to 7.4% subjects at Visit 6 (after the end of the first 3-month treatment course with ulipristal acetate and return to menstruation), before returning to levels similar to screening at Visit 7. The proportion with a thickness >16 mm then decreased to 3.4% at Visit 8.

Hyperplasia was not common in the ulipristal acetate phase III studies.

Over half of patients treated with ulipristal acetate developed non-physiological changes of the endometrium. The proportion of subjects with non-physiological changes did not increase with repeated treatment courses, and this proportion decreased to baseline levels by 3 to 6 months after the end of treatment.

The evaluator considered that the data supports international regulator conclusions regarding safety.

Comments:

Esmya was approved in New Zealand on 7 December 2017. The clinical evaluator's risk benefit assessment is therefore recent and still relevant.

4.2.2 Benefits

For the purposes of this review, the benefits of Esmya (ulipristal acetate) are considered to be:

a. Bleeding reduction

In studies PGL07-021 [5] and PGL07-022 [6], uterine (menstrual) bleeding was assessed with the use of the PBAC. Monthly scores range from 0 (amenorrhea) to more than 500, with higher numbers indicating more bleeding. At screening patients were taught how to use the PBAC and were asked to complete it daily throughout the treatment period up to week 13 and for 28 days preceding the post-treatment follow-up visits and weeks 26 and 38. The PBAC score for a 4-week period was calculated from the sum of the daily PBAC results for 28 days.

The primary end points at week 13 have been taken from Table 2 in study PGL07-021 [5] and Table 2 in study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

b. Fibroid shrinkage

In studies PGL07-021 [5] and PGL07-022 [6], the change in fibroid volume from screening to week 13 was assessed by magnetic resonance imaging. The total fibroid volume was the sum of the individual fibroid volumes.

The end points at week 13 have been taken from Table 2 in study PGL07-021 [5] and Table 2 in study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

c. Fibroid size at week 38

In study PGL07-022 [6], the treatment-free follow-up period required additional visits at weeks 26 and 38. Changes in fibroid volume from screening was assessed.

The secondary safety endpoints have been taken from Table 5 in the supplementary information study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

d. Uterine volume

In studies PGL07-021 [5] and PGL07-022 [6], a reduction in uterine volume (ie, the percentage of women with a least a 25% reduction) was measured.

The end points at week 13 have been taken from Table 2 in study PGL07-021 [5] and Table 2 in study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

e. Amenorrhoea

In studies PGL07-021 [5] and PGL07-022 [6], amenorrhea was measured as a PBAC 28-day score of ≤2 at weeks 9 and 13.

The end points at week 13 have been taken from Table 2 in study PGL07-021 [5] and Table 4 in the supplementary information study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

f. Anaemia

In studies PGL07-021 [5] and PGL07-022 [6], changes in haemoglobin were measured as a secondary endpoint.

The end points at week 13 have been taken from Table 2 in study PGL07-021 [5] and Table 2 in study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

g. Improving quality of life

In studies PGL07-021 [5] and PGL07-022 [6], a number of quality of life scores were measured. Pain was measured with the use of the Short-Form McGill Pain Questionnaire which includes a questionnaire on which scores range from 0 to 45, with higher scores indicating more severe pain

For the purpose of this review, pain was chosen as the effect as it was viewed as more relevant for patients.

The end points at week 13 have been taken from Table 2 in study PGL07-021 [5] and Table 2 in study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

4.2.3 Risks

For the purposes of this review, the risks of Esmya (ulipristal acetate) are considered to be:

a. Liver function test (LFT) increases

The total percentage of hepatic disorders standardised MedDRA query adverse events from the phase III clinical trials have been taken from Table 5 in Annexe 1 and entered into the Effects Table (Table 3) below.

b. Endometrial thickening

In studies PGL07-021 [5] and PGL07-022 [6], endometrial thickness was measured by MRI at screening, at week 13 and if no hysterectomy or endometrial ablation was performed at weeks 26 and 38. In study PGL07-022 [6] is was also measured at week 17.

Endometrial thickness at week 13 has been taken from the Supplementary Table 5 in study PGL07-021 [5] and Table 2 in study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

c. Serious adverse reactions

The frequency and severity of adverse reactions were recorded in studies PGL07-021 [5] and PGL07-022 [6] at every visit.

The number of at least one serious adverse event occurring have been taken from Table 3 in study PGL07-021 [5] and Table 3 in study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

d. Hot flushes

In study PGL07-022 [6], the proportion of patients with moderate-to-severe hot flashes during treatment was recorded.

The numbers for this safety outcome were taken from Table 2 in study PGL07-022 [6] and entered into the Effects Table (Table 3) below.

4.2.4 HiView

HiView is a computer modelling program that supports the appraisal and evaluation of different options helping to identify decisions.

For the purpose of this review, the benefits and risks for Esmya (ulipristal acetate) (described in detail in section 4.2.2 and 4.2.3 of this report) are shown in the decision tree in Figure 2 and the Effects Table (Table 3).

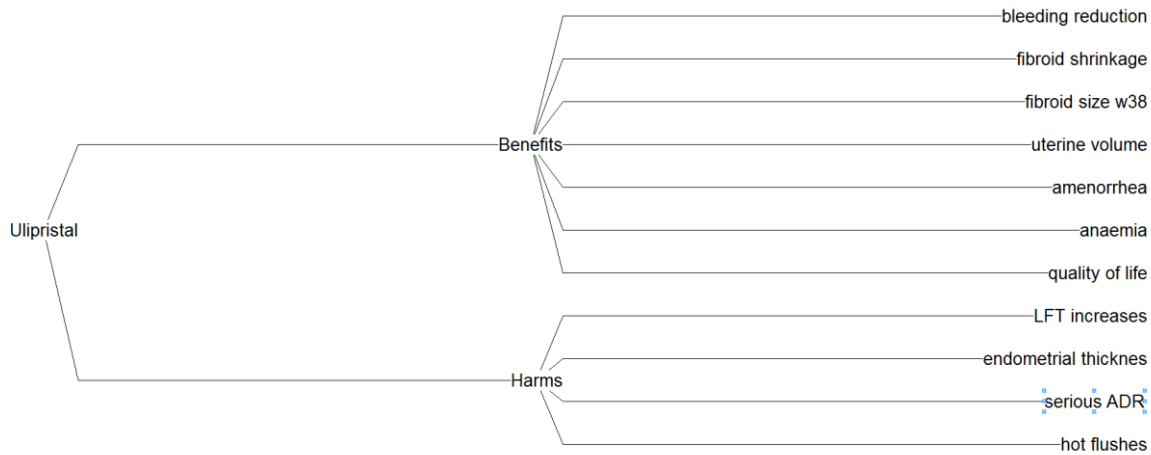


Figure 2: Decision tree for Esmya (ulipristal acetate)

Table 3: Effects table for Esmya (ulipristal acetate) for the treatment of symptomatic uterine fibroids before surgery

Effects	Name	Units	Placebo	Ulipristal acetate	Leuprorelin	Weight

Favourable effects (benefits)	Bleeding reduction	% with PBAC score <75	19	90	89	80
	Fibroid shrinkage	% change from the baseline	3	-36	-53	50
	Fibroid size at week 38	% change at week 38	0*	-45	-17	50
	Uterine volume	% change from the baseline	6	-20	-47	25
	Amenorrhea	%	6	75	80	35
	Anaemia	g/dl	12.6	12.8	12.7	30
	Quality of Life	Short-Form McGill Pain Questionnaire score	-2.5	-5	-5.50	40
Unfavourable effects (risks)	LFT increases	% of patients	1	3.7	2	90
	Endometrial thickness	mm	8	9.4	5.10	11
	Serious adverse reactions	Number	6	8	6	10
	Hot flushes	% of moderate to severe incidences	0*	11	40	20
*0 indicates that the effect wasn't measured in study PGL07-021 [5]						

The data in Table 3 was entered into the computer model with the following results.

Figure 3 shows the relative contributions of effect to the overall preference. The column with the greatest height is the preferred option (ie, leuprorelin). Ulipristal acetate is more favourable than placebo.

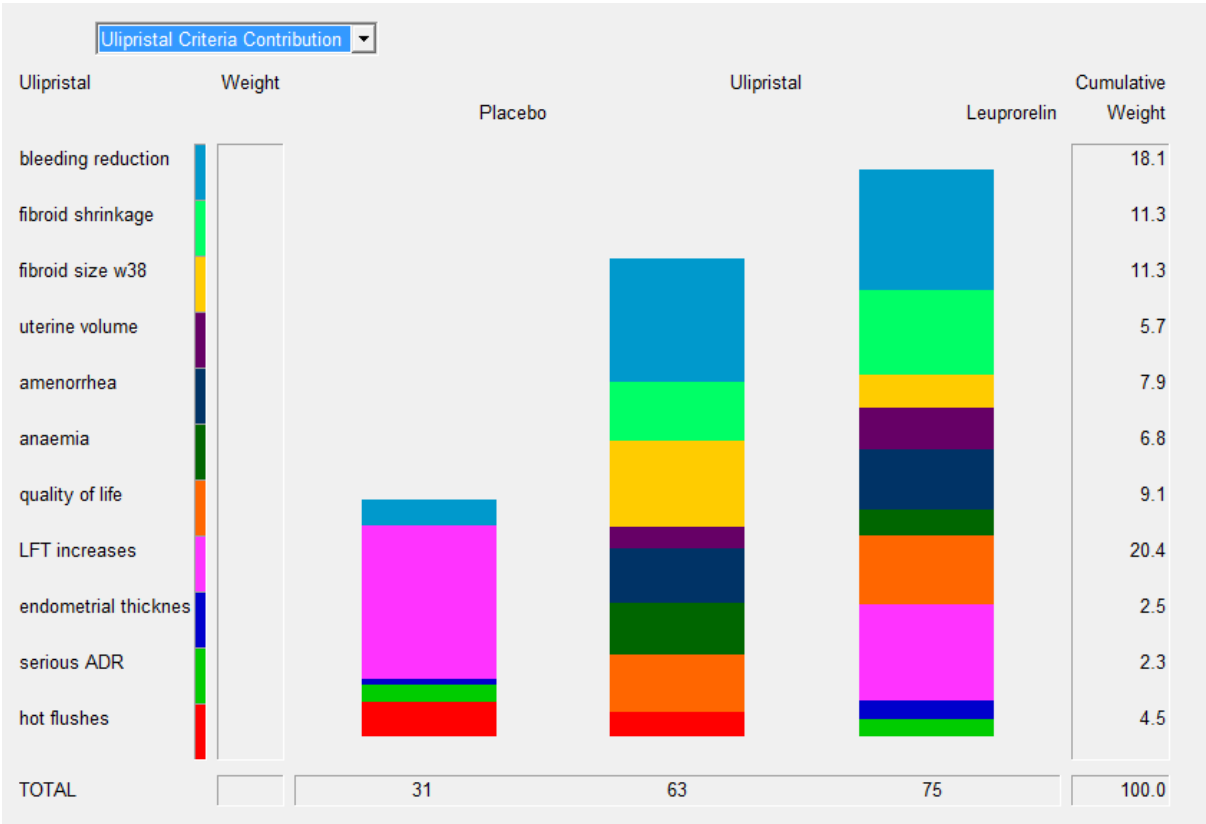


Figure 3: Added-value bar graph for placebo, ulipristal acetate and leuprorelin

The number under the column gives an overall score. A medicine with only favourable effects and no unfavourable effects would score 100 in this computer model. Conversely, a medicine with no favourable effects and only unfavourable effects would score 0.

The numbers in the right hand column in Figure 3 give the relative weight of each effect contributing to the overall model. The effects carrying the most weight are bleeding reduction and drug induced liver injury.

The added-value bar graph in Figure 3 gives an overall comparison of the options, however it is easier to see the difference in the difference displays (Figures 4, 5 and 6 below).

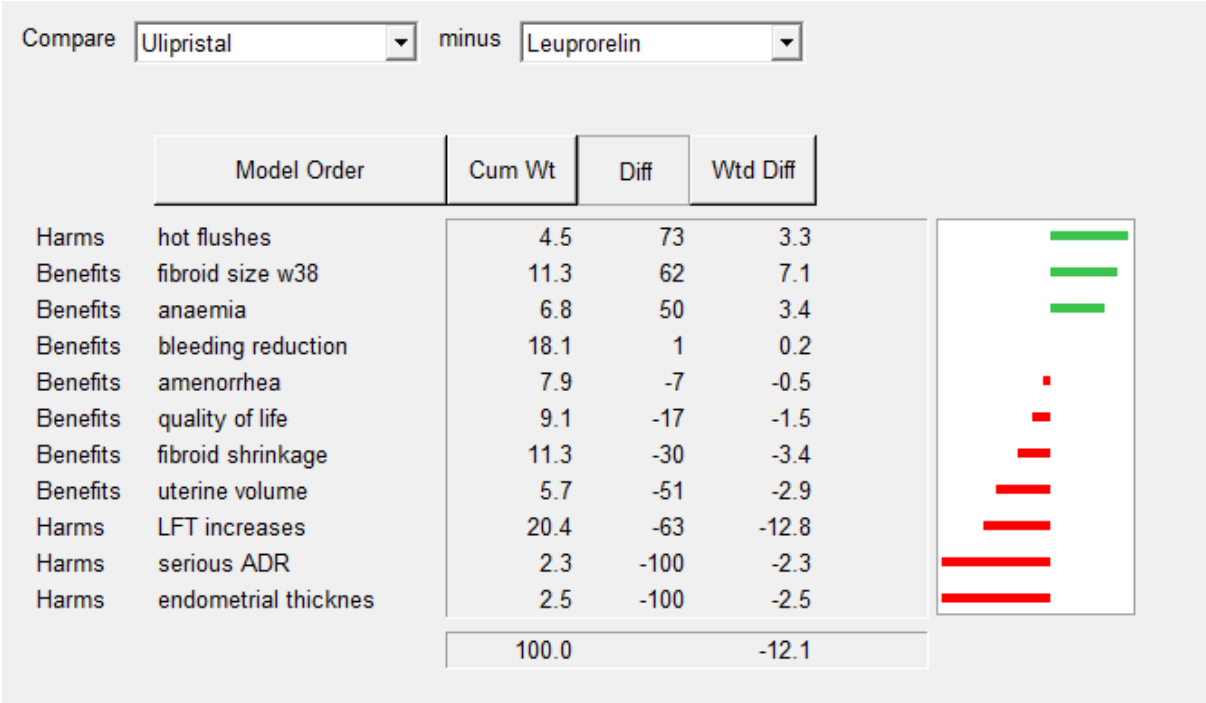
In Figures 4, 5, and 6, the first column of figures shows the cumulative weights normalised so the products sum to 100. The Diff column shows the difference in the original preference values assigned to the options on each criterion. The third column shows each difference multiplied by that criterion's cumulative weight. The weighted differences show the clinical relevance of the difference.

Compare Ulipristal minus Placebo

	Model Order	Cum Wt	Diff	Wtd Diff
Benefits	fibroid size w38	11.3	100	11.3
Benefits	anaemia	6.8	100	6.8
Benefits	amenorrhea	7.9	93	7.4
Benefits	quality of life	9.1	83	7.6
Benefits	bleeding reduction	18.1	71	12.9
Benefits	fibroid shrinkage	11.3	70	7.9
Benefits	uterine volume	5.7	49	2.8
Harms	hot flushes	4.5	-28	-1.2
Harms	endometrial thicknes	2.5	-33	-0.8
Harms	LFT increases	20.4	-100	-20.4
Harms	serious ADR	2.3	-100	-2.3
		100.0		31.9

Figure 4: Difference display of ulipristal acetate and placebo (green bars indicate effects that are better with ulipristal acetate and red bars indicate effects that are better with placebo)

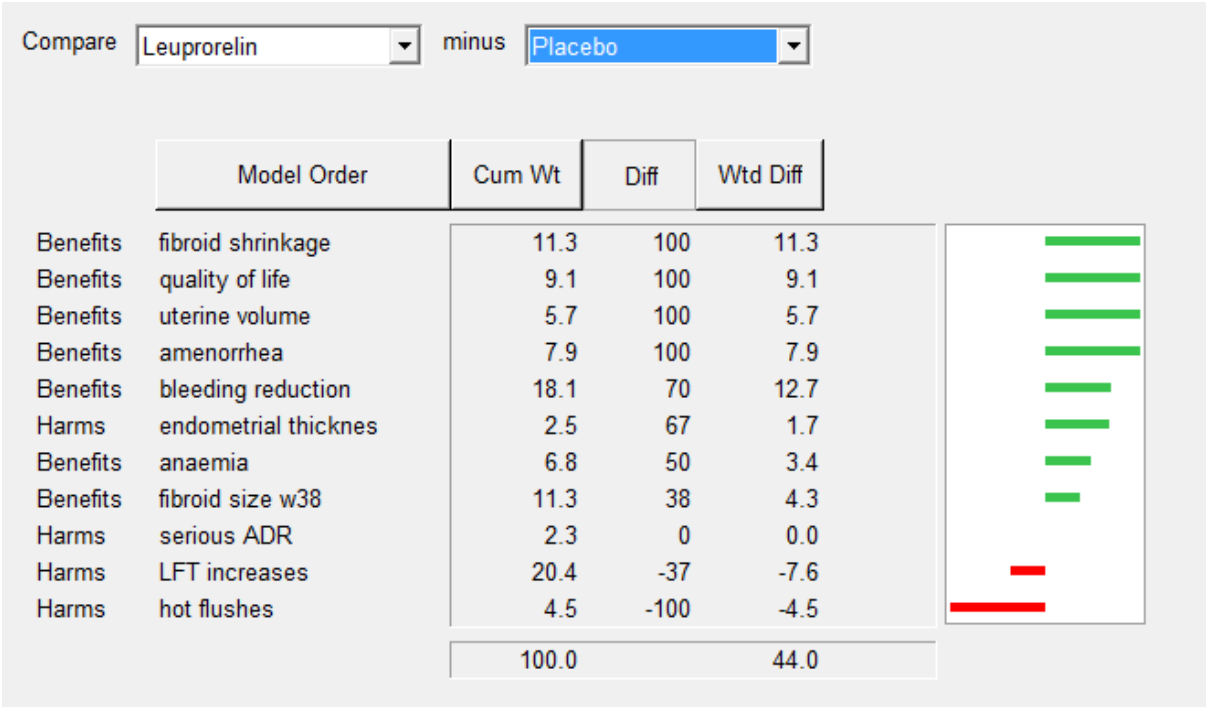
Figure 4 shows that the main favourable effects of ulipristal acetate compared to placebo are fibroid size at week 38 and anaemia. The main unfavourable effects are serious adverse reactions and liver function test increases.



	Model Order	Cum Wt	Diff	Wtd Diff
Harms	hot flushes	4.5	73	3.3
Benefits	fibroid size w38	11.3	62	7.1
Benefits	anaemia	6.8	50	3.4
Benefits	bleeding reduction	18.1	1	0.2
Benefits	amenorrhea	7.9	-7	-0.5
Benefits	quality of life	9.1	-17	-1.5
Benefits	fibroid shrinkage	11.3	-30	-3.4
Benefits	uterine volume	5.7	-51	-2.9
Harms	LFT increases	20.4	-63	-12.8
Harms	serious ADR	2.3	-100	-2.3
Harms	endometrial thicknes	2.5	-100	-2.5
		100.0		-12.1

Figure 5: Difference display of ulipristal and leuprorelin (green bars indicate effects that are better with ulipristal acetate and red bars indicate effects that are better with leuprorelin)

Figure 5 shows that the effects that are better for ulipristal acetate compared to leuprorelin are hot flushes, fibroid size at week 38 and anaemia. The effects that are worse for ulipristal acetate compared with leuprorelin are endometrial thickness, serious adverse reactions, liver function test increases, uterine volume, fibroid shrinkage and quality of life.



	Model Order	Cum Wt	Diff	Wtd Diff
Benefits	fibroid shrinkage	11.3	100	11.3
Benefits	quality of life	9.1	100	9.1
Benefits	uterine volume	5.7	100	5.7
Benefits	amenorrhea	7.9	100	7.9
Benefits	bleeding reduction	18.1	70	12.7
Harms	endometrial thicknes	2.5	67	1.7
Benefits	anaemia	6.8	50	3.4
Benefits	fibroid size w38	11.3	38	4.3
Harms	serious ADR	2.3	0	0.0
Harms	LFT increases	20.4	-37	-7.6
Harms	hot flushes	4.5	-100	-4.5
		100.0		44.0

Figure 6: Difference display of leuprorelin and placebo (green bars indicate effects that are better with leuprorelin and red bars indicate effects that are better with placebo)

Figure 6 shows that the main favourable effects of leuprorelin compared to placebo are fibroid shrinkage, quality of life, uterine volume and amenorrhea. The main unfavourable effects are hot flushes and liver function test increases.

Finally, the computer model can also perform sensitivity analyses. Figure 7 below shows one of these sensitivity analyses. In this analysis the model looks to see if changing any of the outcomes, either the data or the weighting, will affect which is the preferred option. The coloured bars, when shown, indicate by how much the cumulative weight must change for a different option to become the most preferred (green more than 15 points, yellow between 5 and 15 points and red less than 5 points). This analysis is a test of the robustness of the model for the preferred option

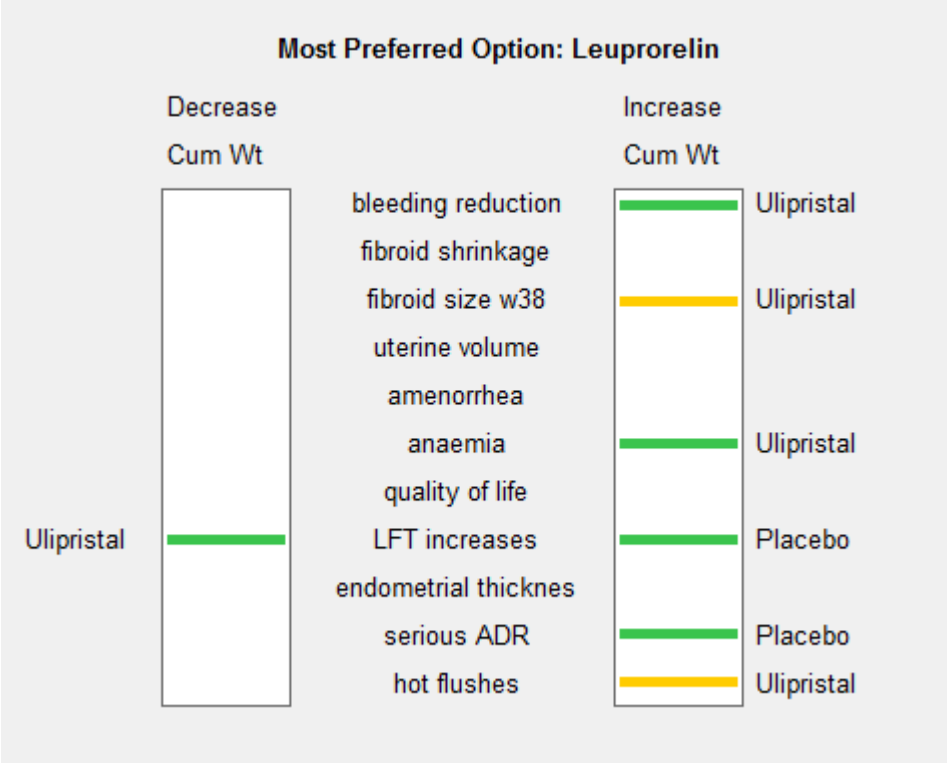


Figure 7: Model sensitivity analyses on the cumulative weights separately for each of the effects

In the current model leuprorelin is the preferred option, however if the weighing was changed for the outcomes of fibroid size after treatment and/or hot flushes ulipristal acetate may become the preferred option. Overall the computer model shows that both ulipristal acetate and leuprorelin have favourable benefit risk profiles as they are both easily preferred to placebo treatment.

Comments:

The Committee has seen this computer modelling program before. At the 158th meeting in June 2014, the Committee was presented with two papers that used the computer model HiView (Consideration of hydroxyethyl starch containing medicines under section 36 of the Medicines Act 1981 and Benefit risk review of strontium) [9].

The computer model can be investigated further in the meeting.

5.0 DISCUSSION AND CONCLUSIONS

Esmya (ulipristal acetate) was approved recently in New Zealand on 7 December 2017 for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

At the previous meeting the Committee reviewed the available information on the possible risk of drug induced liver injury with Esmya (ulipristal acetate) and recommended that Medsafe conduct a benefit risk review under section 36 of the Medicines Act 1981.

This paper presents the information received from the company after issuing a section 36 notice, a benefit risk review by the company and a benefit risk review by Medsafe using the computer model HiView. [redacted]. Medsafe's review also concluded with a favourable benefit risk balance

The balance of benefits and risks for Esmya (ulipristal acetate) was considered favourable only recently when the medicine was approved for use in New Zealand. However, since then a number of cases of drug induced liver injury reported with a temporal association to ulipristal acetate use were considered by the Committee to have potentially impacted this balance.

In this review it was seen that ulipristal acetate treatment has a significant benefit for women with fibroids, reducing the size of the fibroid and improving quality of life. Although there is an alternate treatment, this is not suitable for all women and not all women are suitable for surgery. In addition, it was noted that:

- ulipristal acetate does not cause hot flushes to the extent of leuprorelin treatment
- the effects on fibroid size last longer with ulipristal acetate
- treatment can continue for longer with ulipristal acetate which may be advantageous for women not recommended for surgery.

The potential risk of liver injury is the main risk along with inappropriate treatment for the reversible effects on the endometrium.

In Europe, the PRAC has made recommendations to minimise this risk which include monitoring liver function tests before, during and after treatment and including information in the medicine pack to inform patients of monitoring requirements and symptoms of liver injury (see section 2.2 of this report for full details).

The Committee is asked to advise whether any of these recommendations should also be implemented in New Zealand.

6.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The balance of benefits and risk for the use of Esmya (ulipristal acetate) for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age is favourable.
- Any regulatory action is required (eg, that the recommendations from the PRAC are also implemented in New Zealand) to improve the balance of benefits and risks.

7.0 ANNEXES

1. Medsafe. 2018. *Ulipristal acetate and drug induced liver injury* (March 2018).
2. Medsafe. 2018. *Section 36 notice concerning Esmya (ulipristal acetate) 5 mg tablets* (22 March 2018).
3. Vifor Pharma. 2018. *Section 36 notice concerning Esmya (ulipristal acetate) 5 mg tablets* (23 March 2018).
4. Gedeon Richter. 2018. *Periodic Safety Update Report No. 9* (20 April 2018).
5. Medsafe. 2017. *Medical Advisor Report – Esmya 5 mg (ulipristal acetate)* (July 2017).

8.0 REFERENCES

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8. Donnez J, Hudecek R, Donnez O, et al. 2015. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. *Fertility and Sterility* 103(2): 519-527. URL: www.sciencedirect.com/science/article/pii/S0015028214022985?via%3Dihub (accessed 5 June 2018).
9. Medsafe. 2014. *Minutes of the 158th Medicines Adverse Reactions Committee meeting – 12 June 2014*. URL: http://www.medsafe.govt.nz/profs/adverse/Minutes158.htm (accessed 11 June 2018).