London Medicines Evaluation Network Review

Ulipristal acetate (Esmya®) for the pre-operative and intermittent treatment of moderate to severe uterine fibroids in women of reproductive age. December 2015

Summary

Background and licensed indication	Esmya® (ulipristal acetate 5mg tablets) was launched in April 2012 for pre-operative treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age. In May 2015, the license was further extended to allow intermittent treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age.
Dosing	Oral dose of 5mg once daily for treatment courses of up to 3 months each. To date, repeated intermittent treatment has been studied up to 4 intermittent courses. The first course is started during the first week of menstruation; re-treatment courses should start, at the earliest, during the first week of the second menstruation following the previous treatment course completion.
Alternatives	Surgery, particularly hysterectomy, predominates as the long-term treatment strategy. The levonorgestrel-releasing intrauterine system (LNG-IUS), NSAIDs, tranexamic acid and combined oral contraceptive pills are used to manage menorrhagia and/or dysmenorrhoea. Gonadotropin releasing hormone (GnRH) agonists, goserelin, leuprorelin or triptorelin can be used pre-operatively for 3 to 6 months.
NICE	No relevant NICE guidance available.
Clinical studies	• PEARL I and II: Initial marketing authorisation was based on these studies in which 3 months of ulipristal 5mg or 10mg daily was superior to placebo (PEARL I) and non-inferior to leuprorelin (PEARL II) for reducing excessive uterine bleeding before surgery. Fewer hot flushes occurred with ulipristal vs. leuprorelin. • In PEARL III, the proportion of women in amenorrhoea after each ulipristal 10mg treatment course (primary endpoint) was 80%, 89%, 88% and 90% after the 1st, 2nd, 3rd and 4th course respectively. Uterine fibroid volume decreased by 50%, 63%, 67% and 72% for each course respectively and pain improved. • In PEARL IV, the percentage of patients in amenorrhoea (primary efficacy endpoint) after ulipristal 5mg treatment courses 1 and 2 (Part I) was 62% and after all 4 treatment courses (Part II), it was 49%. In patients taking ulipristal 10mg daily, the percentage of patients in amenorrhoea was 73% (part I) and 61% (part II) respectively. The decrease in fibroid volume from baseline was similar for 5mg and 10mg groups.
Safety	Common adverse effects (≥2%) were mild to moderate in intensity and include headache, hot flushes, nasopharyngitis, abdominal pain, influenza, breast pain/tenderness/discomfort, nausea, fatigue and pelvic pain. GnRH agonists can lead to hot flushes and decreases in bone mineral density whereas ulipristal has a lower incidence of these side effects. Ulipristal can thicken the endometrium and Progesterone receptor modulator Associated Endometrial Changes (PAEC), histological changes in the endometrium, could occur. Repeated courses of ulipristal do not increase the appearance or frequency of PAEC and such changes are rapidly reversible. Data from PEARL III and IV show that the frequency of (mostly reversible) endometrial hyperplasia after 4 courses was lower (0.89%) than the baseline incidence prior to treatment (1.82%).
Convenience	GnRH agonists are administered by monthly subcutaneous injections by healthcare professionals, whereas oral ulipristal would not require this. Long-term ulipristal may replace surgery, e.g. to preserve fertility.
Risk assessment	Treatment with ulipristal for >3 months poses a risk of developing endometrial hyperplasia which should not be mistaken for PAEC. Prescribers have been provided with educational material to avoid inappropriate management of this. Periodic monitoring of the endometrium (e.g. with annual ultrasound) is recommended in patients who receive repeated intermittent treatment. The safety of ulipristal beyond 4 intermittent treatment courses is currently unknown but the PEARL extension 2 study will provide data for up to 8 intermittent courses.
Budget impact	See table below
Funding	The likely commissioning pathway is through CCGs but there are elements of shared care (e.g. monitoring)
Suggested place in therapy	Esmya® maintains its place in therapy for the pre-operative management of uterine fibroids. Surgery (e.g. hysterectomy, myomectomy) may not be a suitable option for all patients, e.g. if the woman wants to preserve fertility or if she is perimenopausal and would rather wait for symptoms to decrease as a result of menopause. Thus, continued medical treatment of fibroids would be valuable in these circumstances.

Drug	Basic NHS list price			
	Per pack (28 tablets or 1 injection)	3 months treatment	6 months treatment	>12 months treatment
Esmya® 5mg	£114.13	£343.39	£686.78 (2x3months)	£1373.56 (4x3months)
Leuprorelin 3.75mg	£75.24	£225.72	£451.44	Not licensed >6m
Triptorelin 3mg	£69.00	£207.00	£414.00	Not licensed >6m
Goserelin 3.6mg	£65.00	£195.00	Not licensed >3m	Not licensed >3m

1. Background and introduction

In April 2012 ulipristal acetate (Esmya®) was launched in the UK for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment was initially limited to one course of 3 months but in December 2013, the license was extended to allow two 3 month courses. In April 2015, the license was further extended to allow the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.[1;2]

Uterine fibroids (leiomyomas) are benign, hormone-sensitive tumours which occur in 20-40% of women of reproductive age.[3;4] Fibroids are three times more common in African-American women than in Caucasian American women.[3] Most women with fibroids do not have symptoms, whilst some remain undiagnosed.[5] The most common symptoms of uterine fibroids are pelvic pain, pelvic pressure and menorrhagia, which can result in iron-deficiency anaemia.[3;5] Fibroids may also lead to infertility, miscarriage, pre-term deliveries and complications in late pregnancy.[5] Overall, around 20-50% require clinical intervention and management is pharmacological or surgical.[5]

Pharmacological management of uterine fibroids

The NICE Heavy Menstrual Bleeding (HMB) guideline recommends a trial of the levonorgestrel-releasing intrauterine system (LNG-IUS) as first line treatment for women with HMB who have fibroids <3 cm in size, provided long-term (at least 12 months) use is anticipated.[6] The (LNG-IUS) has local and systemic hormonal effects, including prevention of endometrial proliferation, thickening of cervical mucus and suppression of ovulation in a small minority of women. NSAIDs can be used to reduce menstrual blood loss and dysmenorrhoea and tranexamic acid reduces heavy bleeding.[5;7] Combined oral contraceptive pills can be used to control menorrhagia and dysmenorrhoea but can increase fibroid size because the fibroids are oestrogen-dependent.[7] Gonadotrophin-releasing hormone (GnRH) agonists reduce hormonal stimulation of fibroids and can reduce fibroids to approximately 25-50% of their size within 3 months, but the fibroids re-grow to their former size within 3-6 months of stopping treatment. GnRH agonists can also cause amenorrhoea, menopausal symptoms and bone loss.[5] NICE guidance recommends that use of GnRH agonists for 3-4 months should be considered prior to a hysterectomy or myomectomy when fibroids are causing an enlarged or distorted uterus.[6] Some GnRH agonists are licensed for the reduction of uterine fibroids in women with heavy bleeding, prior to surgery, but can only be used for up to 3 months (goserelin) or 6 months (triptorelin and leuprorelin).[8]

Surgical management of uterine fibroids

Surgery is indicated when the uterus is greatly enlarged, pressure symptoms are present or when medical management cannot control the symptoms.[3] A hysterectomy is the only definitive procedure for the permanent removal of fibroids, but for women who want to have children or retain their uterus, a myomectomy (removal of fibroids) is the alternative procedure.[5;6] A concern with a myomectomy is that the fibroids may reappear and further surgery may be required.[6] In Uterine artery embolisation (UAE), an embolic agent (such as polyvinyl alcohol) is injected into the uterine arteries, flowing preferentially into the fibroid vessels, and ultimately limiting the blood supply to the fibroids, causing them to shrink. It avoids major surgery and preserves the uterus.[5;7]

Ulipristal

Ulipristal is a selective progesterone receptor modulator (SPRM) which has a tissue-specific partial progesterone antagonist effect, acting on progesterone receptors in myometrial and endometrial tissue and depriving uterine fibroids of growth stimulation due to progesterone.[4;9] Ulipristal reduces fibroids through inhibition of cell proliferation and induction of apoptosis.[1]

Treatment with ulipristal (Esmya®) is as an oral tablet of 5mg daily started during the first week of a menstrual cycle and used for up to 3 months.[1] Re-treatment courses should start during the first week of the second menstruation after completion of the previous course. Repeated intermittent treatment has been studied up to 4 intermittent courses.[1]

Note: Ulipristal acetate 30 mg tablet (ellaOne®) was launched in the UK in 2009 and is licensed for emergency contraception only. This is not to be confused with Esmya® 5mg tablets which are only licensed for the management of uterine fibroids.

2. Proposed place in therapy

Esmya® maintains its place in therapy for its original license i.e. the pre-operative management of moderate to severe symptoms of uterine fibroids. The license extension now allows repeated intermittent treatment courses in women in whom surgery is not intended.[2] Although repeated treatment has been studied for up to 4 intermittent courses of 3 month durations; there is no recommended maximum number of courses. The proposed place in therapy for the long and short-term use of ulipristal as suggested by the manufacturer is as follows:[10]

- Pre-surgical management of symptoms in women of reproductive age
- Short-term medical management of symptoms in perimenopausal women until symptoms reduce as a result of menopause
- Short and long-term treatment of symptoms in women who wish to preserve their fertility
- Long-term treatment of symptoms in women with co-morbidities who are not suitable for surgery

In contrast to Esmya®, GnRH agonists are only licensed for pre-surgical treatment and treatment duration with GnRH agonists is limited to 3 months (goserelin) or 6 months (triptorelin and leuprorelin). The limited treatment duration with GnRH agonists is due to suppression of oestrogen and menopausal symptoms including hot flushes, mood swings, loss of libido and loss of bone mineral density.[2]

3. Evidence selected for inclusion

The original license for Esmya® was based on two pivotal randomised, parallel-group, double-blind phase III, 13 week studies: PGL4001 (Ulipristal acetate) Efficacy Assessment in Reduction of Symptoms due to Uterine Leiomyomata (PEARL I and PEARL II). These studies

were classed as class A data in the New England Journal of Medicine. A review of the PEARL I and II studies can be found at http://www.medicinesresources.nhs.uk/GetDocument.aspx?pageId=770494 and are briefly summarised here.

PEARL I and II inclusion and exclusion criteria[4;11]

- Women were aged 18-50 and had a score on the pictorial blood-loss assessment chart (PBAC, see Appendix1) of >100 during days 1-8 of menstruation (range 0-500, higher score indicates more bleeding), a myomatous uterus with a size equivalent to a uterus of ≤16 weeks gestation, at least one fibroid ≥3cm diameter but none >10cm diameter, and a body mass index of 18-40 kg/m^2. In PEARL I, an additional inclusion criterion was fibroid-related anaemia (Hb ≤10.2g/dL). Uterine bleeding was assessed using the PBAC; menorrhagia was defined as a PBAC score of >100 during a menstrual period, corresponding to a blood loss of 80mL.
- Exclusion criteria: history of uterine surgery (except Caesarean section or cervical conisation), endometrial ablation or uterine artery embolisation, history of, or current gynaecological cancer, current endometrial hyperplasia, haemoglobinopathy, severe coagulation disorder, uterine polyp >2cm, ovarian cyst >4cm, previous or current treatment for fibroids with a GnRH agonist, treatment with agents that affect CYP3A4 or those taking progestogens, aspirin, mefenamic acid, anticoagulants, antifibrinolytic drugs or systemic glucocorticoids.[12;13]

PEARL I

PEARL I was a randomised, parallel group, double-blind, placebo controlled, phase 3 trial designed to assess the efficacy and safety of oral ulipristal 5mg and 10mg daily on uterine bleeding and fibroid volume before surgery in 242 women with symptomatic fibroids who were planning to undergo surgery.[4] Patients were randomised 2:2:1 to receive treatment for up to 13 weeks with ulipristal 5mg (n=96), 10mg (n=98) or placebo (n=48) per day, stratified by haematocrit level (≤ or >28%) and race (black or other). Treatment started during the first 4 days of menstruation, and all patients received 80mg iron supplement daily. At baseline, median PBAC scores ranged from 330 to 376. The **co-primary endpoints** were reduction in uterine bleeding (PBAC <75) and change in total fibroid volume from baseline. At 13 weeks, uterine bleeding was controlled (PBAC <75) in 19%, 91% and 92% of women receiving placebo, ulipristal 5mg and ulipristal 10mg respectively and median total fibroid volume changes from baseline were +3%, -21.2% and -12.3% in these respective groups. Amenorrhoea, pain and quality of life were amongst the **secondary endpoints**. Amenorrhoea (PBAC ≤2) was achieved in 6%, 73% and 82% of women receiving placebo, ulipristal 5mg and ulipristal 10mg respectively; occurring within 10 days in the majority of patients receiving ulipristal. Self-reported pain and discomfort associated with fibroids improved significantly with ulipristal compared to placebo. The adverse effect profile of ulipristal was similar to that of placebo.[4;12] The study was limited by the short duration of treatment; and did not assess treatment-related differences in surgical outcomes.

PEARL II

PEARL II was a randomised, parallel group, double-blind, double dummy, active controlled, phase 3 trial which aimed to assess the efficacy and adverse effects of ulipristal vs. leuprolide acetate (leuprorelin) for treating symptomatic uterine fibroids prior to surgery.[11] Patients were randomised 1:1:1 to receive either 5mg (n=98) or 10mg (n=104) ulipristal daily plus an intramuscular saline injection (placebo) once a month; or placebo tablets plus a 3.75mg leuprorelin acetate injection once a month (n=101). Treatment was started within 4 days after the start of the menstrual period and continued until week 13, when patients could have surgery. The **primary endpoint** was reduction in uterine bleeding (PBAC <75). At 13 weeks, uterine bleeding was controlled (PBAC <75) in 90% of women receiving ulipristal 5mg, 98% receiving ulipristal 10mg and in 89% receiving leuprorelin. **Secondary endpoints** included fibroid volume, pain, quality of life and haemoglobin levels. Fibroid volume was reduced by 36%, 42% and 53% in those receiving ulipristal 5mg, ulipristal 10mg and leuprorelin respectively and rates of amenorrhoea (PBAC ≤2) were 75%, 89% and 80% for these respective groups. Amenorrhoea was induced quickly in ulipristal-treated patients, with bleeding attenuated up to 2 weeks earlier than with leuprorelin. All three groups showed similar improvements in pain, quality of life and haemoglobin levels. Moderate to severe hot flushes were reported in 11% of patients receiving ulipristal 5mg, 10% receiving ulipristal 10mg and 40% receiving leuprorelin; and serum oestradiol levels were 64pg/mL with ulipristal 5mg, 61pg/mL with ulipristal 10mg and 25pg/mL with leuprorelin. Overall, the study demonstrated non-inferior efficacy of ulipristal vs. leuprorelin for reducing excessive uterine bleeding due to uterine fibroids prior to surgery but superior tolerability for hot flushes and oestradiol levels **(primary safety endpoints)**.[11;13] The study limitations were similar to those of PEARL I.

Data to support license extension of ulipristal for repeated intermittent treatment of uterine fibroids

The extension of the license for Esmya® to include the intermittent treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age was based on data from two further long-term phase III studies[14;15]:

- Study PGL09-026 and its extension PGL09-027 (PEARL III and PEARL III extension): multicentre, open-label clinical trials which evaluated the sustained efficacy and safety of four repeated 3 month courses of ulipristal 10mg daily for the long-term treatment of symptomatic uterine fibroids. Each course was followed by a randomised, double-blind placebo controlled period of 10 days treatment with norethisterone acetate or placebo.
- Study PGL11-006 (PEARL IV): multicentre, randomised, double-blind clinical trial which assessed the sustained efficacy and safety of two (part 1) or four (part 2) repeated 3 month courses of ulipristal 5mg or 10mg daily for the long-term treatment of symptomatic uterine fibroids.

PEARL III and PEARL III extension

The aim of **PEARL III** and its extension was to assess the sustained effects of long-term intermittent treatment with ulipristal 10mg daily on the symptoms of uterine bleeding, fibroid size, pain and quality of life after the first treatment course (PEARL III) and after each of up to three more treatment courses (PEARL III extension).[14] The study also aimed to assess the clinical benefit of norethisterone acetate (NETA) 10mg daily administered after each treatment course to reverse the anti-progesterone effect of ulipristal on the endometrium termed

Progesterone receptor modulator Associated Endometrial Changes (PAEC) and its effect on post-treatment menstrual bleeding.[14]

PEARL III was conducted at 21 investigation centres in four European countries from July 2010 to November 2011, and 18 centres also participated in the extension protocol until January 2013. The study enrolled a total of 209 pre-menopausal women with symptomatic uterine fibroids and heavy bleeding. All women received open-label treatment with ulipristal 10mg daily, started during the first 4 days of menstruation. Each treatment course was equal to 90 days of treatment. Approximately 8 weeks into the first treatment course, women were randomised to receive 10 days of double-blind treatment with either NETA 10mg daily or matching placebo at the end of the treatment period allocated randomly in a 1:1 ratio. After completion of the first treatment period, patients were given the option to participate in the PEARL III extension study and receive three further ulipristal treatment courses. A total of 132 patients entered into the extension phase of the study and 107 of these started all four treatment courses. The women participating in the extension study also received the same double-blind treatment with NETA or placebo throughout all treatment courses. Efficacy analyses were conducted on the intention to treat (ITT) population.[14]

Inclusion criteria included premenopausal women aged 18 to 48 years who are eligible for surgery with[14]:

- Body mass index (BMI) 18–40 kg/m^2
- Regular menstrual cycles of 22–35 days with FSH ≤20 IU/L
- At least one fibroid ≥3cm in diameter and none >10cm
- Heavy menstrual bleeding (PBAC score > 100 during days 1–8 of menstruation)
- Uterine size <16 weeks of gestation
- Eligible for fibroid surgery

The key exclusion criteria were[14]:

- Previous uterine surgery including endometrial ablation or uterine artery embolisation
- History of or current uterus, cervix, ovarian, or breast cancer
- Significant finding on Papanikolaou test (PAP) smear within the past 12 months
- Endometrium hyperplasia or adenocarcinoma within the past 6 months or similar lesions in the screening biopsy. In case of biopsies older than 6 months, these had to be repeated
- Large uterine polyp (>2 cm)
- Calcified fibroids and/or a calcified uterus
- Severe coagulation disorder
- One or more ovarian cysts ≥4 cm diagnosed by ultrasound
- History of treatment for fibroid with an SPRM, including ulipristal
- Treatments with progestogens (systemic or progestogen-releasing intrauterine system), oral contraceptive, acetylsalicylic acid, mefenamic acid, anticoagulants such as coumarins and/or antifibrinolytic drugs such as tranexamic acid, systemic glucocorticoid treatments and/or systemic depot glucocorticoid, P-glycoprotein substrates (such as digoxin, fexofenadine) and moderate or potent inhibitors or inducers of CYP3A4

The **Primary efficacy endpoint** was the proportion of patients in amenorrhoea at the end of each ulipristal treatment course. Amenorrhea was defined as no bleeding for a continuous period of at least 35 days (1 day of spotting was allowed within any 35-day interval). Bleeding was assessed using a semi-quantitative bleeding scale, which included four categories: ''no bleeding,'' ''spotting,'' ''bleeding,'' or ''heavy bleeding.''[14] **Secondary endpoints** are described below.

Key results

Table 1: Efficacy results for PEARL III extension[14;16]

	1st course - Daily Ulipristal 10mg	2nd course - Daily Ulipristal 10mg	3rd course - Daily Ulipristal 10mg	4th course - Daily Ulipristal 10mg	3 month follow-up
Primary endpoints					
Amenorrhoea, n/N (%)	105/132 (79.5)	116/131 (88.5)	105/119 (88.2)	96/107 (89.7)	-
Spotting or no bleeding, n/N (%)	117/132 (88.6)	123/131 (93.9)	112/119 (94.1)	100/107 (93.5)	-
Mean (median) time to amenorrhea, days (range)	9.4 (4.0) (0-57)	3.3 (2.0) (0–32)	5.3 (3.0) (0–49)	4.2 (3.0) (0–40)	-
Secondary end points					
% Change in median volume of three largest fibroids from baseline.	-49.9 (n=130)	-63.2 (n=119)	-67.0 (n=106)	-72.1 (n=96)	-58.8 (n=97)
Total reduction ≥25%, n (%)	101 (77.7)	95 (79.8)	83 (78.3)	79 (82.3)	70 (72.2)
Total reduction ≥50%, n (%)	65 (50.0)	77 (64.7)	66 (62.3)	67 (69.8)	56 (57.7)
% Change in median uterine volume from baseline	-29.8 (n=132)	-32.3 (n=121)	-29.9 (n=107)	-40.2 (n=96)	-22.3 (n=99)
Total reduction ≥25%, n (%)	73 (55.3)	73 (60.3)	61 (57.0)	64 (66.7)	45 (45.5)
Short-Form McGill Pain score, median	1.0 (n=131)	1.0 (n=119)	1.0 (n=108)	1.0 (n=96)	2.0 (n=96)
Short-Form McGill Pain score, change from baseline, median	-7.0 (n=131)	-6.0 (n=119)	-5.0 (n=108)	-6.0 (n=96)	-4.0 (n=96)

UFS-QoL questionnaire, symptom severity, mean ± SD	13.4 ±15.3 (n=129)	18.4±16.8 (n=117)	20.5±19.5 (n=104)	17.9±17.1 (n=91)	27.1± 21.1 (n=98)
UFS-QoL questionnaire, symptom severity, change from baseline, mean ± SD	-35.8±21.2 (n=129)	-30.5±21.9 (n=117)	-27.7±23.3 (n=104)	-30.0±20.3 (n=91)	-21.2±22.1 (n=98)
UFS-QoL questionnaire, health-related total QoL score, mean ± SD	87.8±14.8 (n=131)	85.2±16.4 (n=117)	85.2±18.1 (n=108)	87.5±16.2 (n=96)	79.2±22.9 (n=99)
UFS-QoL questionnaire, health-related total QoL score, change from baseline, mean ± SD	32.8±21.9 (n=131)	29.6±22.4 (n=117)	29.4±23.4 (n=108)	31.4±21.6 (n=96)	22.7±22.5 (n=99)

Table 2: Menstrual bleeding; ulipristal followed by placebo vs. ulipristal followed by NETA[16]

PBAC scores (see Appendix1) during days 1 – 8 of menses, median		**Total**	**Ulipristal then placebo**	**Ulipristal then NETA**	***P* value**
Baseline (post screening)		*n* = 132	*n* = 69	*n* = 63	-
	Median score	235	228	257	
After 1st course		*n* = 131	*n* = 69	*n* = 62	
	Median score	94	123	59	
	Median change	-120	-92	-144	0.006
After 2nd course		*n* = 123	*n* = 65	*n* = 58	
	Median score	64	84	54	
	Median change	-150	-127	-171	0.01
After 3rd course		*n* = 114	*n* = 58	*n* = 56	
	Median score	42	75	28	
	Median change	-131	-103	-224	<0.0003
After 4th course		*n* = 89	*n* = 49	*n* = 40	
	Median score	31	55	13	
	Median change	-120	-97	-166	0.02

Notes[14]*:*

- *Amenorrhea (and spotting or no bleeding) assessed during ulipristal treatment. For remaining results, courses 1 and 4 data were collected at the end of UPA treatment; courses 2 and 3 data were collected after the first menstrual bleed after UPA treatment and subsequent NETA/placebo treatment.*
- *n = Number of women with non-missing observations*
- *On the UFS-quality of life (QoL) questionnaire, scores for symptom severity range from 0 – 100, higher score indicating increased severity. Total scores for health-related QoL range from 0 to 100, with higher scores indicating a better QoL.*

Summary of PEARL III studies

In summary, the PEARL III studies showed that intermittent treatment with ulipristal 10mg daily was associated with high rates of amenorrhoea with a trend towards higher rates with each additional course. The median time to amenorrhoea after the start of the 2nd, 3rd and 4th courses ranged between 2 to 4 days. Menstrual bleeding measured by the PBAC score reduced progressively after the start of the 1st course until after the end of the 4th course. Ulipristal 10mg daily also led to a reduction in fibroid volume and there was further reduction with successive treatment courses, with no evidence of rapid rebound regrowth. Women reported substantial improvements in pain and QoL scores during treatment. Most adverse events were mild or moderate. NETA did not affect PAEC but was associated with significantly reduced and earlier occurrence of, menstrual bleeding during off-treatment periods.

PEARL IV

The aim of PEARL IV was to compare and assess the sustained efficacy of two (part 1) or four (part 2) repeated 12-week treatment courses of ulipristal 5mg or 10mg daily for the long-term management of symptomatic uterine fibroids; and to assess the overall tolerability of repeated courses of ulipristal.[2;15] PEARL IV was conducted at 46 study sites across 11 European countries from June 2012 to December 2014. The study enrolled a total of 451 premenopausal women with symptomatic uterine fibroids and heavy bleeding. Women were allocated randomly by a web-integrated voice response system in a 1:1 ratio to receive either 5mg or 10mg daily of ulipristal or matching placebo. Treatment was started during the first 4 days of menstruation and each treatment course lasted 12 weeks (84 days). Treatment courses were separated by a drug-free period until the start of the second menstruation following the end of the previous treatment course.

The Full Analysis Set 1 (FAS 1) defined as all randomised patients who received study medication at least once during treatment course 1 was the primary interest for the efficacy analysis. Analysis of primary efficacy endpoints and fibroid volume was also conducted on FAS 2, 3 and 4 (i.e. randomised patients who received study medication at least once during treatment course 2, 3 and 4 respectively). The study would have a power greater than 85% to detect an absolute difference in the primary endpoint between the two treatment groups.

The **Primary efficacy endpoint** was the percentage of patients in amenorrhoea at the end of both treatment courses 1 and 2 (Part I) and at the end of all four treatment courses (Part II) defined as no more than 1 day of spotting within a 35-day interval. **Secondary endpoints**

are described below.

Key results

Table 3: Efficacy results for PEARL IV[2;15]

Primary endpoints	Ulipristal 5mg N = 228	Ulipristal 10mg N = 223	Difference (95% CI) (ulipristal 10mg vs. 5mg)	*P* value
Number of patients in amenorrhoea at the end of treatment courses (1 **and** 2), no. (%)	n = 197 122 (61.9%)	n = 187 136 (72.7%)	10.8% (1.5% – 20.1%)	0.032
Number of patients in amenorrhoea at the end of treatment courses 1, 2, 3 **and** 4, no. (%)	n = 195 95 (48.7%)	n = 185 112 (60.5%)	11.8% (1.9% – 21.8%)	0.027

Secondary endpoints	Treatment course	Ulipristal 5mg daily	Ulipristal 10mg daily	Difference (95% CI) (ulipristal 10mg vs. 5mg)	*P* value
Patients in amenorrhoea at the end of treatment course	After course 1	n =216 155 (71.8%)	n = 207 171 (82.6%)	10.8% (2.9% - 18.8%)	0.011
	After course 2	n = 205 152 (74.1%)	n = 197 162 (82.2%)	8.1% (0.1% - 16.1%)	0.066
	After course 3	n = 225 165 (73.3%)	n = 221 173 (78.3%)	4.9% (-3.0% - 12.9%)	0.267
	After course 4	n = 227 158 (69.6%)	n = 220 164 (74.5%)	4.9% (-3.4% - 13.2%)	0.290
Mean (median) time to amenorrhoea at the start of each course (days)	Treatment course 1	n = 155 10.8 (5.0)	n = 171 8.3 (4.0)	- -	- -
	Treatment course 2	n = 149 10.5 (5.0)	n = 161 9.0 (6.0)	- -	- -
	Treatment course 3	n = 161 15.8 (6.0)	n = 166 15.5 (6.0)	- -	- -
	Treatment course 4	n = 154 16.6 (5.0)	n = 155 16.2 (5.0)	- -	- -
Patients with controlled bleeding in the last 56 days of treatment	1 **and** 2	n = 185 150 (81.1%)	n = 172 148 (86.0%)	- 5% (-2.7% - 12.6%)	- 0.263
	1,2,3 **and** 4	n = 158 106 (67.1%)	n =146 105 (71.9%)	- 4.8% (-5.5% - 15.2%)	- 0.430
PBAC post-treatment, median change from baseline	After course 2	n = 152 -95	n = 146 -109.5	- -	- -
	After course 4	n = 140 -118	n = 138 -121	- -	- -
Median change in fibroid volume from baseline (3 largest myomas)	After course 2	n = 198 -54.1%	n = 200 -58.0%	- -	- -
	After course 4	n = 166 -71.8%	n = 170 -72.7%	- -	- -
n (%) with fibroid volume reduction ≥25%	After course 2	159 (80.3%)	156 (83.0%)	-	-
	After course 4	135 (81.3%)	150 (88.2%)	-	-
Median change in uterine volume from baseline	After course 2	n = 205 -23.6%	n = 203 -25.5%	- -	- -
	After course 4	n = 170 -25.1%	n = 171 -30.7%	- -	- -
n (%) with uterine volume reduction ≥25%	After course 2	98 (47.8%)	103 (50.7%)	-	-
	After course 4	85 (50.0%)	97 (56.7%)	-	-

Notes:

- *n = Number of women with non-missing observations*
- *Controlled bleeding was defined as no episodes of heavy bleeding and a maximum of 8 days of bleeding during the last 56 days of a course of treatment.*

Summary of PEARL IV

In summary, the results of PEARL IV were consistent with those obtained in PEARL III and PEARL III extension. Long-term intermittent treatment with ulipristal 5mg or 10mg daily led to amenorrhea after each treatment course and controlled bleeding (no episodes of heavy bleeding and a maximum of 8 days of bleeding during the last 56 days of treatment course) after all four treatment courses in a clinically significant proportion of patients. PBAC scores associated with return of menstruation decreased after each subsequent treatment course. Both fibroid volume and uterine volume decreased during the study, pain and QoL scores improved. Most adverse effects were mild or moderate. The results are considered to be of clinical relevance and support repeated intermittent treatment with ulipristal.

4. Critical evaluation

4.1.Clinical application

A major strength of the PEARL III and IV studies was the well-defined primary endpoint of amenorrhoea which was having no more than 1 day of spotting within a 35-day interval and the European Medicines Agency (EMA) considers this to be clinically relevant.[2] In comparison, the co-primary endpoints for PEARL I were percentage of patients with a PBAC score <75 at end of treatment and change in total fibroid volume[4]; and for PEARL II, the primary endpoint was the percentage of patients with a PBAC score <75 at end of treatment.[11] Although the PEARL trials have assessed both 5mg and 10mg doses of ulipristal, the licensed dose is 5mg daily. This was selected because no significant differences in efficacy or safety were observed between 5mg and 10mg. The manufacturer confirmed that that the decision to evaluate the 10mg dose in PEARL III was made before the outcomes from earlier trials were obtained which showed no major differences between the two doses. The 10mg dose was evaluated in Pearl IV as an appropriate comparator to the licensed 5mg dose.[17]

It was not possible to use placebo controls to evaluate long-term treatment with ulipristal in the PEARL III and IV studies but PEARL I and II demonstrated that ulipristal is superior to placebo and non-inferior to leuprorelin. The size of the largest fibroid was restricted to a maximum diameter of 10 cm in PEARL I, II and III and 12 cm in PEARL IV; and the maximum uterus size permitted was the same size as for 16 weeks gestation. Therefore the effect of ulipristal on larger fibroids and/or larger uterus is unknown. The study population consisted of relatively few black women which may be considered an important limitation of these studies since the incidence of fibroids is greater in this demographic group. Another limitation is that long-term treatment with ulipristal for uterine fibroids has only been studied for up to 4 intermittent courses over a period of 18 months. This means that at present, we still don't know the efficacy and safety of ulipristal beyond this period. Additional data will be obtained from the ongoing PEARL extension 2 trial of up to 8 repeated intermittent treatment courses with ulipristal 10mg daily.

As mentioned previously, GnRH agonists are the other medical treatment licensed for the management of fibroids. In PEARL II, ulipristal was shown to be non-inferior to leuprorelin for reducing excessive uterine bleeding associated with uterine fibroids prior to surgery and superior with regards tolerability to leuprorelin for hot flushes and estradiol levels. PEARL III and IV studies have now demonstrated the efficacy and safety of ulipristal used as long-term intermittent therapy for up to a period of 18 months which now offers further advantages compared to GnRH agonists. The use of GNRH agonists is limited to 3 to 6 months for the pre-operative treatment of uterine fibroids whereas ulipristal's license now covers repeated intermittent therapy whether surgery is planned or not.

4.2.Safety

4.3.Key adverse events

PEARL III and IV

Similar to previous studies, the most frequently reported adverse event was headache (3 to 20% in PEARL III and 2 to 11% in PEARL IV). The majority were mild or moderate in intensity. Other commonly reported side effects (≥2%) in PEARL III and/or IV studies included hot flushes, nasopharyngitis, abdominal pain, influenza, breast pain/tenderness/discomfort, nausea, fatigue and pelvic pain. Overall, adverse reactions were less frequent in subsequent treatment courses than during the first one, with no increase in frequency of any adverse event over time. The safety profile was comparable between the 5mg and 10mg groups. Seven women (5.3%) in PEARL III and 28 women (6.1%) in PEARL IV experienced at least one serious adverse event (SAE). The most frequently reported SAE in both studies was excessive uterine bleeding; which could be expected given that the population studied were women with fibroid-related heavy menstrual bleeding. Other SAEs reported in PEARL III and/or PEARL IV were thyroid cyst, chlamydia and fibroid expulsion. Five women (3.8%) in PEARL III and 32 women (7%) in PEARL IV discontinued the study due to adverse effects. Some reasons for discontinuation included heavy uterine bleeding, vertigo, dyspepsia, abdominal cramps, high blood pressure, uterine leimyoma, endometriosis, bipolar disorder and changes to laboratory parameters. In either PEARL III or IV, no safety concerns were identified from physical examination, vital signs, laboratory safety tests, ovarian ultrasound, and electrocardiograms. The safety assessments show overall that the intermittent repeated administration of ulipristal was well tolerated.[2;14;15]

4.4 Risk assessment

Effects of ulipristal on the endometrium

Endometrial thickness

Due to the mechanism of action of ulipristal, benign thickening of the endometrium (≥ 16mm) is expected and may occur in 10–15% of patients. In the PEARL studies, the effect was transient and was less frequently observed in subsequent treatment courses. Endometrial thickening reverses when treatment is stopped and menstruation resumes. If endometrial thickening is noted, which persists after return of menstruation during off-treatment periods or beyond 3 months following the end of treatment courses, and/or an altered bleeding pattern is noted (see SPC), investigation including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.[1;2]

Progesterone Receptor Modulator Associated Endometrial Changes

SPRMs have been associated with a pattern of benign, non-physiological, non-proliferative, histological features of the endometrium. These changes are referred to as Progesterone Receptor Modulator Associated Endometrial Changes (PAEC).[14] They do not fit into any existing standard diagnostic group and differ from a classic unopposed oestrogen effect.[18] Features of PAEC may include[2]:

- Epithelial changes (further classified as secretion, mitoses or apoptotic changes)
- Presence of extensive cysts
- Unusual vascular changes (further classified as chicken-wire capillaries, thick-walled vessels or ectatic vessels)

These non-physiological changes have been observed in approximately 60% of patients treated with ulipristal for 3 months. A lower

frequency was observed with subsequent treatment courses and within 3 to 6 months after the end of treatment, the frequency reduced to baseline levels demonstrating the reversibility of PAEC. Results from PEARL III and IV studies showed that repetition of treatment courses did not increase PAEC appearance, frequency or reversibility. Ten days of norethisterone did not have a significant impact on the incidence of PAEC induced by ulipristal. From the study results there is no evidence that PAEC is a precursor to or a risk factor for more serious conditions of the endometrium such as endometrial carcinoma.[1;2] At present there are no specific recommendations for the management of PAEC. PAEC is not to be confused with endometrial hyperplasia (see below).

Endometrial hyperplasia

Endometrial hyperplasia is an irregular proliferation of the endometrium (i.e. greater than the normal proliferation that occurs during the menstrual cycle) which may progress to or coexist with endometrial cancer.[19;20] It can be classified into two groups; (i) hyperplasia without atypia and (ii) hyperplasia with atypia.[21] For hyperplasia without atypia, the risk of progression to carcinoma is less than 5% and majority will regress spontaneously. The risk of progression to carcinoma in atypical hyperplasia is around 30%.[20]

In studies of repeated intermittent treatment with ulipristal, a total of 7 cases of hyperplasia (3 atypical) were observed out of 789 patients with adequate biopsies (0.89%). This incidence was lower than that in the study population prior to treatment (1.82%). The majority of cases spontaneously reversed to normal endometrium under continued treatment and/or during the follow-up period and the incidence did not increase during subsequent treatment courses. The observed frequency was in line with prevalence reported in literature for pre-menopausal women (2% to 25.3% with 0.03% to 1.26% for atypical hyperplasia). Overall, the risk of endometrial hyperplasia associated with ulipristal is considered to be low. The manufacturer advises that if hyperplasia without atypia occurs, the patient should be monitored as per usual clinical practice (e.g. a follow-up control 3 months later. In case of atypical hyperplasia, investigation and management as per usual clinical practice should be performed.[1;2] To avoid mistaking PAEC for hyperplasia, educational material has been supplied to prescribers and pathologists and relevant warnings and recommendations have been provided in the SPC.[1]

Long-term effects on the endometrium

There still remains a degree of uncertainty in the knowledge of the unfavourable long-term effects of ulipristal since this has only been studied up to 4 intermittent treatment courses. Additional safety data will be collected in a post-authorisation safety study following 1,500 patients who intend a long-term treatment with ulipristal for up to 5 years as well as from an ongoing study PGL11-024 (PEARL extension 2 (the second extension of PEARL III) which will provide safety and efficacy data of up to 8 treatment courses of ulipristal 10mg.[2]

Treatment course beyond three months

Some women who obtain symptomatic relief (e.g. less bloating and discomfort due to reduced fibroid size and better energy due to less heavy bleeding) might be inclined to use ulipristal persistently without a break. Continued use poses a risk since intermittent use allows/induces a type of withdrawal bleed, which should offset any developing endometrial hyperplasia. The SPC indicates that each treatment cycle should not be longer than 3 months as the effect on endometrium is unknown if continued longer.[1;2]

Periodic monitoring of the endometrium (e.g. with annual ultrasound) is recommended with repeated intermittent treatment with ulipristal. The relevant warnings and recommendations relating to endometrial safety have been provided in the SPC.[1]

4.5. Potential advantages and disadvantages over existing technologies

4.5.1 Convenience

- Ulipristal appears to have a better tolerability profile compared to GnRH agonists which have drawbacks of profound oestrogen deficiency, a greater incidence of hot flushes and can lead to a decrease in bone mineral density.
- Ulipristal is given orally whereas GnRH agonists are given by monthly injections. Oral therapy provides an option which patients may find more acceptable.
- Oral therapy with ulipristal will reduce the time and cost of healthcare professionals who currently administer the injections.
- The duration of treatment with GnRH agonists is limited to 3 to 6 months due to their adverse effects whereas studies have demonstrated the safety and efficacy of long-term treatment with ulipristal (up to 4 intermittent courses over 18 months). In addition, the effects of ulipristal were found to be sustained after treatment cessation/ during off-treatment periods with no evidence of rebound growth.
- Long-term treatment with ulipristal may totally replace surgery in some cases and may become a treatment option for some women wishing to avoid surgery in the future.

4.5.1. Healthcare resource utilisation

Oral treatment will reduce hospital attendance for monthly subcutaneous injections, reducing cost and time of doctors and nurses. Annual ultrasound is required in patients receiving repeated intermittent treatment. No other specific routine monitoring is recommended by the manufacturer other than as dictated by clinical practice e.g. 3 month follow-up for patients with hyperplasia (without atypia). There might be a need for additional appointments to review treatment and the patient's clinical condition.

4.5.2. Suitability for shared care

Ulipristal should be initiated by a specialist whether it is used pre-operatively or for long-term intermittent treatment. Aspects of monitoring e.g. ultrasound would take place in secondary care but there may be elements of shared care.

4.5.3. Drug cost and likely budgetary impact[22]

Table 4

Population (England)	Total Number	Number Per 100,000 Female Population
Fibroid Population: Number of women diagnosed with uterine fibroids in secondary care	38,488	143
Number of women with a diagnosis of fibroids that had a procedure	20,080	74*
Number of women potentially eligible for medical management with Esmya®	10,040	37
Ulipristal costings		
Costs per intermittent course per woman	£343.39	£12,705.43
Annual cost per woman requiring an average of 2 courses per year	£686.78	£25,410.86**
Procedure costings (for comparison)		
Laparoscopic hysterectomy MA08	£2,205.00	
Total hysterectomy Q074	£3,322.26	
Myomectomy Q092	£3,213.00	
Ablation MA127	£905.00	
Diagnostic hysteroscopy MA21Z	£501 to £905	
Therapeutic hysteroscopy MA12Z		
Uterine Artery Embolisation (UAE,RC41Z)	£2,458	

Notes

- All data obtained from England Health Episode Statistics (HES) (2013/2014)
- *Derived by dividing the number of procedures carried out in England by the total female population in England (27 million), then multiplied by 100,000.
- ** The licensed treatment regime for Esmya® consists of 3 months on treatment and then a minimum of 2 menses before the next course. Following this pattern, the estimated average number of courses per year per woman is 2 courses. The off-treatment interval may be longer for some women.

Assumptions

- Half of the total population of England is female based on the pattern of the total UK population.
- About 50% of women who had a procedure would be eligible for medical management with Esmya®

Table 5: Basic NHS costs

Treatment	Dose	Cost
Ulipristal (Esmya®)	5mg orally daily for treatment courses of up to 3 months each[1]	£114.13 per month[8]
Goserelin (Zoladex)	3.6mg by SC injection every month for a maximum of 3 months, in women who have anaemia due to uterine fibroids, prior to surgery.[8]	£65.00 per 3.6mg injection[23]
Leuprorelin acetate (Prostap SR DCS)	3.75mg by SC or IM injection every month for 3-4 months (max 6 months), to reduce size of uterine fibroids and associated bleeding prior to surgery.[8]	£75.24 per 3.75mg injection[23]
Triptorelin (Decapeptyl SR)	3mg by IM injection every month for at least 3 months, max 6 months, to reduce size of uterine fibroids.[8]	£69.00 per 3mg injection[8]
Cost of laparoscopic hysterectomy		£2,205[24]

Table 6: Comparative budget impact

Drug	Basic NHS list price			
	Per pack (28 tablets or 1 injection)	3 months treatment	6 months treatment	>12 months treatment
Esmya® 5mg	£114.13	£343.39	£686.78	£1373.56
Leuprorelin 3.75mg	£75.24	£225.72	£451.44	Not licensed >6m
Triptorelin 3mg	£69.00	£207.00	£414.00	Not licensed >6m
Goserelin 3.6mg	£65.00	£195.00	Not licensed >3m	Not licensed >3m

5. Health Economics

No health economic data were identified.

6. Likely commissioning and funding pathway

The likely commissioning pathway is through CCGs but there are elements of shared care (e.g. monitoring).

7. Suggested place in therapy

Esmya® maintains its place in therapy for the pre-operative management of uterine fibroids and now additionally to reduce need for invasive surgery (e.g. hysterectomy, myomectomy) which may not be a suitable option for all patients, e.g. for medical or personal reasons, if the woman wishes to preserve her fertility or if the woman is perimenopausal and would rather wait for the symptoms of uterine fibroids to decrease as a result of menopause. Thus, a continued medical treatment of fibroids would be valuable and currently no other medical treatment is approved for relative long-term management of this condition.

Written by Elizabeth Uhegwu, Medicines Information Pharmacist London Medicines Information Centre, Northwick Park Hospital, Watford Road, Harrow, Middlesex, HA1 3UJ. E-mail: e.uhegwu@nhs.net . The LMEN would like to thank Sarah Cavanagh from Ipswich Hospital NHS Trust and Dr Alvan Priddy, Consultant Gynaecologist, LNWH NHS Trust for comments on this review. Gedeon Richter UK has commented on this review.

Embase: ULIPRISTAL/ AND UTERUS MYOMA
Medline: ulipristal.af and LEIOMYOMA/

Reference List

(1) Summary of Product Characteristics. Esmya 5 mg Tablets (ulipristal acetate). Gedeon Richter UK. Date of revision of the text: 27/05/2015 via http://www.medicines.org.uk
(2) Committee for Medicinal Products for Human Use (CHMP). Assessment report (license extension): Esmya, ulipristal acetate. Reference EMA/CHMP/84021/2015, April 2015 via www.ema.europa.eu
(3) Payne, J. Fibroids. Document ID: 1236, version 27 via www.patient.co.uk <Accessed 20/01/15>
(4) Donnez J, Tatarchuk TF, Bouchard P et al. Ulipristal acetate versus placebo for fibroid treatment before surgery (PEARL I). N Engl J Med 2012; 366(5):409-420.
(5) Denby A. London New Drugs Group review: Ulipristal (Esmya®) for the pre-operative treatment of moderate-to-severe uterine fibroids. 2012 via http://www.medicinesresources.nhs.uk/GetDocument.aspx?pageId=770494
(6) National Collaborating Centre for Women's and Children's Health. Clinical Guideline 44, Heavy menstrual bleeding. January 2007 via http://www.nice.org.uk
(7) Duhan N. Current and emerging treatments for uterine myoma - an update. International Journal of Women's Health 2011; 3:231-241.
(8) British National Formulary (online) London: BMJ Group and Pharmaceutical Press. Available at:http://medicinescomplete.com <Accessed 26/08/2015>
(9) Committee for Medicinal Products for Human Use (CHMP). Summary of opinion (initial authorisation). Esmya, ulipristal acetate. Reference EMA/679632/2011, December 2011 via www.ema.europa.eu
(10) Personal communication with Gedeon Richter, 12/08/2015
(11) Donnez J, Tomaszewski J, Vázquez F et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. (PEARL II). N Engl J Med 2012; 366(5):421-432.
(12) Donnez J, Tatarchuk TF, Bouchard P et al. Supplementary appendix: Ulipristal acetate versus placebo for fibroid treatment before surgery. (PEARL I). N Engl J Med 2012; 366(5). http://www.nejm.org/
(13) Donnez J, Tomaszewski J, Vázquez F et al. Supplementary appendix: Ulipristal acetate versus leuprolide acetate for uterine fibroids. (PEARL II). N Engl J Med 2012; 366(5). http://www.nejm.org/
(14) Donnez J, Vázquez F, Tomaszewski J et al. Long-term management of uterine fibroids with ulipristal acetate. (PEARL III and PEARL III Extension). Fertility and Sterility 2014; 101(6):1565-1573.
(15) Donnez J, Hudecek R, Donnez O et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. (PEARL IV) (Part 1). Fertility and Sterility 2014; 103(2):519-527.
(16) Donnez J, Vázquez F, Tomaszewski J. Supplementary appendix: Long-term management of uterine fibroids with ulipristal acetate. (PEARL III and PEARL III Extension). Fertility and Sterility 2014; 101(6):1573.e1-1573.e18.
(17) Personal communication with Gedeon Richter, 21/01/2016
(18) Tafi E, Scala C, Maggiore U et al. Drug safety evaluation of ulipristal acetate in the treatment of uterine fibroids. Expert Opin Drug Saf 2015; 14(6):965-977.
(19) Giuntoli, RL. and Zacur, HA. Management of endometrial hyperplasia via www.uptodate.com <Accessed 24/11/2015>
(20) Endometrial hyperplasia. Patient UK via http://patient.info/doctor/endometrial-hyperplasia <Accessed 25/11/2015>
(21) Emons G, Beckmann MW, Schmidt D et al. New WHO Classification of Endometrial Hyperplasias. Geburtshilfe Frauenheilkd 2015; 75(2):135-136.
(22) Personal communication with Gedeon Richter, 16/11/2015
(23) Department of Health, Welsh Government. National Health Service England and Wales. Drug Tariff October 2015. TSO, London., 2015.http://www.drugtariff.nhsbsa.nhs.uk/#/00252860-FA/FA00251932/Home
(24) Enhanced Tariff Option 2015/16 NHS England via https://www.england.nhs.uk/wp-content/uploads/2015/03/2015-16-eto-spreadsheet.xlsx <Accessed 12/12/2015>

Appendix 1: PBAC score[4]

- The pictorial blood-loss assessment chart (PBAC) is a validated method used to assess menstrual blood loss.
- The PBAC score ranges from 0 to more than 500 (with no defined upper limit).
- Menorrhagia was defined as a PBAC score >100 during one menstrual period, corresponding to a blood loss of >80mL.
- Patients record the number of tampons or sanitary pads they use and the extent of soiling with blood.