

New Medicine Recommendation for

Ulipristal acetate (Esmya®) for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age

Recommendation: Amber 0 - prescribing of first month's treatment by secondary care specialists with continued supply from Primary Care

Ulipristal acetate is recommended for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age in Lancashire only when the first month's supply is prescribed by a specialist within secondary care (e.g. gynaecologist) in the pre-surgical or intermittent treatment setting. Additional cycles of treatment may be prescribed in the Primary Care setting when supported with a prescribing information sheet. Treatment should only be initiated after failure of standard first line therapies.

Summary of supporting evidence

- Ulipristal is an orally active progesterone receptor antagonist that deprives uterine fibroids of growth stimulation. It is the first oral preparation to be licensed for this indication. [1]
- As ulipristal treatment does not suppress oestrogen synthesis, its use is not associated with menopausal symptoms and bone loss, unlike GnRH agonists. [2]

Pre-Surgery Setting

- In the pre-surgery setting, ulipristal was demonstrated to be noninferior to leuprorelin for controlling uterine bleeding at week 13 of the PEARL II study [3] Uterine bleeding was controlled in 90% (84/93) and 89% (82/92) of patients in the ulipristal 5mg and leuprorelin groups respectively. The difference between the groups was 1.2% (95% confidence interval (CI): -9.3% to 11.8%)
- The median reduction in volume of the three largest fibroids at week 13 was 36% and 53% in the ulipristal 5mg and leuprorelin groups, respectively. A significantly greater median reduction in uterine volume was achieved in the leuprorelin group (47%) compared with the ulipristal 5mg group (20%). Excess bleeding was controlled significantly more rapidly in patients receiving ulipristal 5mg compared with those receiving leuprorelin, $p < 0.001$. Amenorrhoea was induced more rapidly in ulipristal-treated patients: median time to amenorrhoea was 7 days vs 21 days
- The PEARL I study showed that, at week 13, bleeding was controlled in 91% (86/94) of patients who received ulipristal 5mg compared with 19% (9/48) of patients receiving placebo, $p < 0.001$. Fibroid volume reduced by a mean of 21% in patients who received ulipristal 5mg compared with 3.0% for placebo ($p = 0.002$). Amenorrhoea was achieved in 73% [69/94] of patients with ulipristal 5mg compared to 6% [3/48] for placebo ($p < 0.001$).
- In the pre-surgery setting, the total cost per patient for ulipristal acetate is £619 versus £682 for GnRH agonists (goserlin), representing a saving of £63 over the 3-4 month time horizon.

Intermittent Use Setting

- Ulipristal is the first pharmacological treatment to be licensed for the longer-term management of patients with symptomatic uterine fibroids by allowing repeated intermittent treatment courses in women who are not intending to undergo surgery. [4]
- Intermittent treatment with ulipristal has the potential to avoid surgery/other invasive

procedures or to delay them or allow less invasive procedures. This would be beneficial for many patients with symptomatic fibroids. This population includes younger women who may wish to become pregnant in the future, women with other medical conditions who are not fit to undergo surgery and do not have any options after treatment with currently available drugs, and peri-menopausal women who may choose to have intermittent oral medical treatment instead of invasive procedures until menopause itself makes further treatment unnecessary.

- The PEARL IV study, which compared 5mg and 10mg (unlicensed) doses of ulipristal showed that amenorrhoea, at the end of treatment courses 1 and 2 was 62% (122/197) for the 5mg dose and 73% (136/187) for the 10mg dose. The difference (10mg group minus 5mg group) was 11% (95% CI: 1.5% to 20%; p=0.032).
- The proportions of patients in amenorrhoea at the end of all four treatment courses was 49% (95/195) for the 5mg group and 61% (112/185) for the 10mg group. The difference was 12% (95% CI: 1.9% to 22%; p=0.027). There was no significant difference between treatment groups for the secondary outcome of controlled bleeding. [4]
- Quality of life was measured using the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QoL) and the Euro-QoL-5D (EQ-5D) questionnaire. The mean symptom severity score (UFS-QoL) at baseline was 48.73, with baseline scores being very similar in the two treatment groups. After four treatment courses, the mean change from baseline in the UFS-QoL symptom severity score was -29.81 in each treatment group. [4] [5]
- Pearl III comprised one course of open-label treatment with once daily 10mg ulipristal (unlicensed dose) for three months and then randomisation in a 1:1 ratio to receive double-blind treatment with norethisterone acetate 10mg orally daily or placebo, for 10 days.
- 78% (164/209) patients achieved amenorrhoea at the end of the first treatment course (95% CI, 72.4%–83.5%).
- The median time to amenorrhea from treatment start was 3.5 days. In the extension study, 88.5%, 88.2%, and 89.7% were in amenorrhea at the end of courses 2, 3, and 4, respectively. The median times to amenorrhea after the start of each course were 2, 3, and 3 days for courses 2, 3, and 4, respectively. The percentages of women with only spotting or no bleeding were 93.9%, 94.1%, and 93.5% at the end of courses 2, 3, and 4, respectively.
- UFS-QoL scores indicated substantially reduced QoL at baseline, but mean scores were within the range of healthy participants at the end of each treatment course and the improvement was largely maintained at 3-month follow-up after the final treatment course. [6]

Safety

- Compared with leuprorelin, ulipristal treatment resulted in a significantly lower incidence of moderate to severe hot flushes and did not reduce oestradiol to post-menopausal levels.
- In the PEARL II study, an adverse event was reported by 77% and 84% of patients in the ulipristal 5mg and leuprorelin groups respectively. Serious adverse events were reported by 8% and 6% of patients respectively. An adverse event led to study drug discontinuation in 1% and 6% of patients respectively.
- In the PEARL I study, an adverse event was reported by 49% and 46% of patients in the ulipristal 5mg and placebo groups respectively. Serious adverse events were reported by 2% and 6% of patients respectively. An adverse event led to study drug discontinuation in 1% and 2% of patients respectively.
- In the PEARL IV study Sixteen patients (3.5%) reported a total of 18 on-treatment serious adverse events and two of these were considered to be treatment-related. Thirteen patients (2.9%) reported 16 off treatment serious adverse events, 11 of which were considered to be treatment-related. The most frequently reported serious adverse event

was menorrhagia (in six patients, five deemed treatment-related). Uterine leiomyoma was reported as a treatment-related serious adverse event in four patients. [5]

Economic Considerations

- The drug acquisition cost of ulipristal is £684.78 for 6 month's treatment. 6 months of equivalent GnRH drugs have acquisition costs as follows: Goserelin £390.00, Leuprorelin £451.44, Triptorelin £414.00 to £490.14. GnRH analogue are administered by injection, the cost of which will need to be factored into their prices to give a true treatment cost per patient.
- In the pre-surgery setting, using the SMC cost model [1] for Lancashire, with an estimated population of around 1.5 million, the estimated acquisition costs for ulipristal in the pre-surgery setting will be as follows:
 - Year 1: £13,312
 - Year 5: £63,602
- SMC analysis suggest that a course of treatment with ulipristal acetate 5 mg is estimated to achieve a cost saving of £59.49 per patient when compared to the cheapest GnRH analogue. For Lancashire, using the SMC model, the following savings can be estimated:
 - Year 1: £1,157
 - Year 5: £5,525
- Using the SMC cost model in the intermittent treatment setting, [7] for Lancashire the estimated acquisition costs for ulipristal will be:
 - Year 1: £46,171
 - Year 5: £242,207

Details of Review

Name of medicine: Ulipristal acetate (Esmya®)
Strength and form: 5 mg Tablets
Dose and administration: 5 mg to be taken orally once daily for treatment courses of up to 3 months each. [8] Treatments should only be initiated when menstruation has occurred: <ul style="list-style-type: none">• The first treatment course should start during the first week of menstruation.• Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion. The treating physician should explain to the patient the requirement for treatment free intervals. Repeated intermittent treatment has been studied up to 4 intermittent courses. 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. [8]
BNF therapeutic class / mode of action: Chapter 6.4.1.2 Progestogens and progesterone receptor modulators > Progesterone receptor modulators [9] Esmya (ulipristal acetate) is an orally-active, synthetic selective progesterone receptor modulator characterised by a tissue-specific partial progesterone antagonist effect. [4] Selective progesterone receptor modulators (SPRMs), e.g. ulipristal, act through progesterone receptors and behave as agonists or antagonists in various target organs. [2] As ulipristal treatment does not suppress estrogen synthesis, its use is not associated with menopausal symptoms and bone loss, unlike GnRH agonists. [2]
Licensed indications: Ulipristal acetate is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age Regulatory background: <ul style="list-style-type: none">• Ulipristal (Esmya®) was granted its initial EU Marketing Authorisation in February 2012 for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age, with a treatment duration limited to 3 months. The treatment duration was limited because of the absence of long term safety data for a period longer than 3 months or for repeat courses of treatment. [4]• In December 2013, the indication was extended to allow two, 3-month treatment courses if deemed appropriate by the treating physician [10]. This was based on the results of the PEARL III and PEARL III extension studies, which investigated the safety and efficacy of up to four, 3-month treatment courses of ulipristal acetate 10 mg. [4]• In May 2015, the license was further extended to allow ulipristal's use for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. [8]
Proposed use: As above

Uterine Fibroids and Heavy Menstrual Bleeding

Uterine fibroids (uterine leiomyoma) are benign, monoclonal, hormone-sensitive, smooth muscle tumours of the uterus. They are the most common tumour of the female reproductive tract in premenopausal women and have been reported to affect 20-40% of women during their reproductive years. [4]

Uterine fibroids are often asymptomatic, but when symptomatic, the primary symptoms are heavy uterine bleeding, anaemia, abdominal pressure, abdominal pain, increased urinary frequency and infertility. [4] The management of uterine fibroids includes “watchful waiting”, medical, interventional, and surgical options. [11]

Symptomatic uterine fibroids are the leading reason for hysterectomy. Hysterectomy is the only treatment that removes fibroids permanently but it may not be a suitable option for all patients, e.g. it is unsuitable for patients who wish to preserve fertility. [4] [7]

Other, less invasive treatment procedures include myomectomy (which may preserve fertility), uterine artery embolization (UAE) and, if the dominant symptom is bleeding, endometrial ablation. [4] [12] The choice of treatment depends on fibroid size, the underlying symptoms and their severity and the woman’s desire for subsequent fertility and pregnancy, as well as efficacy and need for repeated interventions. [2] [7]

Pharmaceutical treatment should be considered where no structural or histological abnormality is present, or for fibroids less than 3 cm in diameter which are causing no distortion of the uterine cavity. [13] The European Menopause and Andropause Society (EMAS) issued a position statement on the management of uterine fibroids outlining the range of medical treatments available including:

- tranexamic acid
- NSAIDs
- GnRH analogues
- levonorgestrel-releasing intrauterine system
- combined oral contraceptives
- norethisterone
- injected long acting progestogens
- selective progesterone receptor modulators [2]

Heavy menstrual blood loss is one of the most frequently disabling symptoms of uterine fibroids. [4] The NICE guideline on Heavy Menstrual Bleeding (CG 44) [13] is similar to the EMAS statement, above, [13] stating that pharmaceutical treatment should be considered where no structural or histological abnormality is present, or for fibroids less than 3 cm in diameter which are causing no distortion of the uterine cavity. If pharmaceutical treatment is appropriate and either hormonal or non-hormonal treatments are acceptable, treatments should be considered in the following order:

- levonorgestrel-releasing intrauterine system
- tranexamic acid
- NSAIDs
- combined oral contraceptives
- norethisterone

When a first pharmaceutical treatment has proved ineffective, a second pharmaceutical treatment can be considered rather than immediate referral to surgery. [7] CG 44 additionally states:

- a GnRH agonist can be considered in all patients prior to hysterectomy and myomectomy and is recommended if the uterine fibroids have caused an enlarged or distorted uterus.

[2] [13] [1]

GnRH-agonists are effective in reducing fibroid-related bleeding, correcting anaemia when given concomitantly with iron therapy, reducing abdominal symptoms and reducing fibroid and uterine volume. Their use is limited to 3-6 months duration as suppression of oestrogen to castration levels results in menopausal symptoms including hot flushes, mood swings/depression, sleep disturbances, vaginal dryness, loss of libido and can also lead to loss of bone mineral density. [4] The improvements resulting from GnRH agonist treatment disappear soon after stopping. [2]

Clinical Evidence

Pre-Surgery Clinical Evidence

Ulipristal is an orally active progesterone receptor antagonist that deprives uterine fibroids of growth stimulation. It is the first oral preparation to be licensed for this indication. [1]

The SMC reviewed and accepted ulipristal for the pre-operative treatment of moderate-to-severe symptoms of uterine fibroids in adult women of reproductive age in January 2013, limited to three months. [1] The AWMSG supported essentially the same indication with similar restrictions in August 2013. [14]

When the SMC reviewed ulipristal in the pre-operative setting, it considered the various GnRH agonists to be of similar efficacy to ulipristal for this indication. [13]

At the time of the SMC's review, ulipristal was only licensed for three months of treatment as there was limited efficacy and safety data beyond three months. In December 2013, after the SMC review, the indication was extended to allow two 3-month treatment courses if deemed appropriate by the treating physician [10]. This was based on the results of PEARL III and PEARL III extension studies which investigated the safety and efficacy of up to four 3-month treatment courses of ulipristal acetate 10 mg. [4]

Evidence to support the use of ulipristal in the pre-operative treatment of uterine fibroids comes from two similarly designed, phase III, multi-centre studies: PEARL I and PEARL II. 5mg and 10mg doses were studied but only the results for the 5mg licensed dose of ulipristal were included in the SMC review.

PEARL II was a double-blind study to evaluate the efficacy and safety of ulipristal compared with leuprorelin that recruited pre-menopausal women aged 18 to 50 years with a score on the pictorial blood-loss assessment chart (PBAC) greater than 100 during days one to eight of menstruation. [3]

The trial participants had a myomatous uterus with a size equivalent to 16 weeks or less of gestation, one or more fibroids ≥ 3 cm diameter and no fibroids >10 cm in diameter. Patients were randomised equally, with stratification for race and ethnic group, to receive ulipristal 5mg or 10mg orally daily with a monthly intramuscular saline injection, or oral placebo daily plus monthly leuprorelin 3.75mg intramuscular injections. Treatment started during the first four days of menstruation and continued until week 13. After week 13, patients could undergo surgery according to the clinical judgement of the investigator.

The primary efficacy endpoint was the proportion of patients with control of uterine bleeding at week 13. This was a non-inferiority study with a pre-specified non-inferiority margin of -20%, based on the lower limit of two-sided 95% confidence intervals.

Uterine bleeding was controlled in 90% (84/93) and 89% (82/92) of patients in the ulipristal 5mg and leuprorelin groups respectively. The difference between the groups was 1.2% (95% confidence interval (CI): -9.3% to 11.8%), therefore non-inferiority was demonstrated. The median reduction in volume of the three largest fibroids at week 13 was 36% and 53% in the ulipristal 5mg and leuprorelin groups, respectively. A significantly greater median reduction in uterine volume was achieved in the leuprorelin group (47%) compared with the ulipristal 5mg

group (20%). Excess bleeding was controlled significantly more rapidly in patients receiving ulipristal 5mg compared with those receiving leuprorelin, $p < 0.001$. Amenorrhoea was induced more rapidly in ulipristal-treated patients: median time to amenorrhoea was 7 days vs 21 days.

Both study groups had a similar improvement in pain scores measured using the short-form McGill Pain Questionnaire. Quality of life was measured using the uterine fibroid symptom and quality of life questionnaire. The mean (\pm standard deviation) change from baseline in the health-related quality of life score was 24 (± 27) and 23 (± 28), respectively.

PEARL I was a placebo controlled double-blind study to evaluate the efficacy and safety of ulipristal. It recruited patients similar to those in PEARL II who also had fibroid-related anaemia. [15] Patients were randomised to receive ulipristal 5mg, 10mg or placebo daily, started during the first four days of menstruation and continued until week 13. After week 13, patients could undergo surgery according to the clinical judgement of the investigator.

The co-primary efficacy endpoints were the percentage of patients with control of uterine bleeding at week 13, as defined in the PEARL II study, and change in total fibroid volume from screening to week 13, assessed by magnetic resonance imaging (MRI). At week 13, bleeding was controlled in 91% (86/94) of patients who received ulipristal 5mg compared with 19% (9/48) of patients receiving placebo, $p < 0.001$. The median (interquartile range) percentage change in total fibroid volume from screening to week 13 was -21 (-41 to -1.1) in patients who received ulipristal 5mg compared with 3.0 (-20 to 23) in patients who received placebo, $p = 0.002$.

Amenorrhoea was achieved in 73% [69/94] of patients with ulipristal 5mg compared to 6% [3/48] for placebo ($p < 0.001$). Change in mean (\pm standard deviation) haemoglobin from baseline to week 13 was 4.2g/dL (± 1.9) in the ulipristal 5mg group and 3.1g/dL (± 1.7) in the placebo group, $p < 0.001$.

The median change in short-form McGill Pain Questionnaire to week 13 was -5.0 (-8.0 to -2.0) for ulipristal 5mg and -2.5 (-6.3 to 1.0) for placebo ($p = 0.10$). Quality of life was measured using a questionnaire assessing discomfort associated with uterine fibroids (range 0 to 28). The median change from baseline to week 13 (interquartile range) was -9.0 (-13.0 to -6.0) and -6.0 (-9.0 to -2.0) for ulipristal and placebo respectively ($p = 0.001$).

Intermittent Use Clinical Evidence

A 2015 license extension allowed ulipristal's use for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. [8] Ulipristal is the first pharmacological treatment to be licensed for the longer-term management of patients with symptomatic uterine fibroids by allowing repeated intermittent treatment courses in women who are not intending to undergo surgery. [4]

The drug's manufacturer requested that the SMC review ulipristal when positioned for use in a second-line setting where patients are unsuitable for, or have failed to respond to, first-line treatment for uterine fibroids and described as being normally focused on the control of heavy menstrual bleeding (HMB). [13] Intermittent use was approved by the SMC in January 2016, and advice was issued stating that a phase III study had demonstrated treatment with the licensed dose of ulipristal acetate controlled uterine bleeding in approximately three-quarters of patients with symptomatic uterine fibroids after four intermittent treatment courses. [7] The AWMSG issued a Preliminary Appraisal Recommendation, mirroring that of the SMC, recommending ulipristal as an option for use within NHS Wales for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. [16]

The main evidence for the license extension to allow ulipristal's intermittent use is from the **PEARL IV** study. [4] [17] Supportive data were from the open-label **PEARL III** study (which used an unlicensed dose of ulipristal) and its extension study. [6] **PEARL IV** was a double-blind,

randomised study of 451 pre-menopausal women aged 18 to 50 years with uterine fibroids with uterus size <16 weeks,^a largest myoma ≥3cm and ≤12cm in diameter. [4] [17] Patients were randomised to receive 5mg (licensed dose) or 10mg once daily ulipristal for four courses of 12 weeks each, separated by drug-free intervals. Previous short term studies showed that ulipristal was superior to placebo in reducing menstrual bleeding and fibroid size (PEARL I study) [15] and was non-inferior to monthly injections of leuprorelin acetate for controlling uterine bleeding (PEARL II study). [3] A placebo arm was considered unethical in the PEARL IV study. [4] The study was fully blinded until the completion of part I (first two treatment courses) then unblinded to the sponsor, statistics and data management personnel. [4]

The primary outcome was the percentage of patients in amenorrhoea, at the end of both treatment courses 1 and 2 (part 1) and at the end of all four individual treatment courses (part 2). Amenorrhoea was defined as no more than one day of spotting within a 35-day interval. Patients recorded their bleeding pattern at screening and after treatment courses 1, 2 and 4 using the validated PBAC self-reporting tool for assessing menstrual blood loss. [17]

Analyses were conducted on 384 patients from the full analysis set (n=451) who had an amenorrhoea assessment at the end of treatment courses 1 and 2. The proportions of patients in amenorrhoea at the end of both treatment courses 1 and 2 in the ulipristal 5mg and 10mg groups were 62% (122/197) and 73% (136/187), respectively; difference (10mg group minus 5mg group) = 11% (95% CI: 1.5% to 20%; p=0.032). The proportions of patients in amenorrhoea at the end of all four treatment courses in the ulipristal 5mg and 10mg groups were 49% (95/195) and 61% (112/185), respectively; difference = 12% (95% CI: 1.9% to 22%; p=0.027). There was no significant difference between treatment groups for the secondary outcome of controlled bleeding. [4]

Median time to amenorrhoea in the 5mg group ranged from six to eight days. There was no significant difference between the treatment groups in reduction of the three largest fibroids from baseline to end of study: 37% (from a baseline of 77cm³) in the 5mg group and 58% (from a baseline of 92cm³) in the 10mg group. Pain reduction, assessed by visual analogue scale was similar in both groups. [4]

Quality of life was measured using the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QoL) and the Euro-QoL-5D (EQ-5D) questionnaire. In the total treatment group, the mean symptom severity score (UFS-QoL) at baseline was 48.73, with baseline scores being very similar in the two treatment groups. A level of 23 assessed by the Euro-QoL-5D (EQ-5D) questionnaire has been cited as normal for healthy women. [17] After four treatment courses, the mean change from baseline in the UFS-QoL symptom severity score was -29.81 in each treatment group. [4] [5]

Improvement in the UFS-QoL total score followed a similar pattern. [4] The EQ-5D questionnaire demonstrated improvements in the pain/discomfort and anxiety/depression dimensions after the first treatment course that were comparable between the two treatment groups. [4]

The lack of an appropriate comparator limits the relevance of the PEARL IV study. There are no efficacy data in the patient population corresponding to the proposed positioning, a second-line setting where patients are unsuitable for, or have failed to respond to all currently available pharmacological treatments for uterine fibroids. [18]

PEARL III included 209 pre-menopausal women aged 18 to 48 years, with at least one fibroid >3cm in diameter and none >10cm, heavy menstrual bleeding, and uterine size <16 weeks of gestation, who were eligible for fibroid surgery. [6] The study comprised one course of open-label treatment with once daily 10mg ulipristal (unlicensed dose) for three months and then randomisation in a 1:1 ratio to receive double-blind treatment with norethisterone acetate 10mg

^a In comparison to a uterus of 16 weeks of pregnancy

orally daily or placebo, for 10 days. Patients could either attend the final follow-up visit 12 weeks later or enter an extension study including three further courses, each separated by an off-treatment period including a full menstrual cycle up to the start of the second menstruation.

The primary outcome was amenorrhoea (defined as for **PEARL IV**) at the end of the treatment course. A total of 78% (164/209) patients achieved amenorrhoea at the end of the first treatment course (95% CI, 72.4%–83.5%). The median time to amenorrhea from treatment start was 3.5 days (interquartile range [IQR], 2–6 days). For the 132 women who entered the extension study to receive multiple treatment courses, 88.5%, 88.2%, and 89.7% were in amenorrhea at the end of courses 2, 3, and 4, respectively. The median times to amenorrhea after the start of each course were 2, 3, and 3 days for courses 2, 3, and 4, respectively. The percentages of women with only spotting or no bleeding were 93.9%, 94.1%, and 93.5% at the end of courses 2, 3, and 4, respectively.

The median change from baseline to end of the first ulipristal treatment course in the combined volume of the three largest fibroids was 45.1% (IQR, 66.1 to 24.9%). During the first treatment course, improvements in pain were apparent from the fifth week onward and were generally maintained for all ulipristal treatment periods. UFS-QoL scores indicated substantially reduced QoL at baseline, but mean scores were within the range of healthy participants at the end of each treatment course and the improvement was largely maintained at 3-month follow-up after the final treatment course. [6]

Safety Summary

The SPC for ulipristal (Esmya®) lists the following adverse events: [8]

Incidence of Event	Adverse Event
Very Common (≥1/10)	Amenorrhea, Endometrial thickening
Common (≥1/100 to <1/10)	Headache, Vertigo, Abdominal pain, Nausea, Acne, Musculoskeletal pain, Hot flush, Pelvic pain, Ovarian cyst, Breast tenderness/pain, Fatigue, weight increase
Uncommon (≥1/1,000 to <1/100)	Anxiety, Emotional disorder, Dizziness, Dry mouth, Constipation, Alopecia, Dry skin, Hyperhidrosis, Back pain, Urinary incontinence, Uterine haemorrhage, Metrorrhagia, Genital discharge, Breast discomfort, Oedema, Asthenia, Blood cholesterol increased, Blood triglycerides increased
Rare (≥1/10,000 to <1/1,000)	Epistaxis, Dyspepsia, Flatulence, Ovarian cyst ruptured, Breast swelling

The co-primary safety endpoints in the **PEARL II** study were serum oestradiol levels at week 13 and the proportion of patients with moderate to severe hot flushes during treatment. The median oestradiol levels at week 13 were 64 picograms/mL (234 picomol/L) in the ulipristal 5mg group and 25 picograms/mL (92 picomol/L) in the leuprorelin group, p<0.001. This represents a decrease to postmenopausal levels in the leuprorelin group. Moderate to severe hot flushes were reported in 11% and 40% of patients respectively, p<0.001.

In the **PEARL II** study, an adverse event was reported by 77% and 84% of patients in the ulipristal 5mg and leuprorelin groups respectively. Serious adverse events were reported by 8% and 6% of patients respectively. An adverse event led to study drug discontinuation in 1% and 6% of patients respectively.

In the **PEARL I** study, an adverse event was reported by 49% and 46% of patients in the ulipristal 5mg and placebo groups respectively. Serious adverse events were reported by 2% and 6% of patients respectively. An adverse event led to study drug discontinuation in 1% and 2% of patients respectively.

The pivotal **PEARL IV** study did not provide comparative safety data versus a relevant

comparator. [4] [17]

Treatment-emergent adverse events (TEAEs) were categorised as being “on-treatment” or “off treatment”. On-treatment events were those that started on or after the first dose of study medication, up to and including seven days after the last dose of study medication within each treatment course. Off-treatment TEAEs were those that started more than seven days after the last dose of study medication within each treatment course and prior to the start of the next treatment course. On-treatment TEAEs were reported in similar numbers of patients receiving 5mg or 10mg ulipristal and were more frequent during the first treatment course than subsequent courses: 44% in both the 5mg and 10mg groups during the first course and 24% and 19%, respectively during the fourth course. [4]

Sixteen patients (3.5%) reported a total of 18 on-treatment serious adverse events and two of these were considered to be treatment-related. Thirteen patients (2.9%) reported 16 off treatment serious adverse events, 11 of which were considered to be treatment-related. The most frequently reported serious adverse event was menorrhagia (in six patients, five deemed treatment-related). Uterine leiomyoma was reported as a treatment-related serious adverse event in four patients. [5]

Ulipristal has a specific pharmacodynamic action on the endometrium and may cause reversible changes in endometrial histology known as Progesterone Receptor Modulator Associated Endometrial Changes (PAEC) which are different from endometrial hyperplasia. In addition, reversible increase of the endometrium thickness may occur during treatment and monitoring, including annual ultrasound, is recommended. [8]

Cost Effectiveness Summary

Pre-Surgery - SMC Cost Effectiveness Review

Ulipristal's manufacturer presented a cost-minimisation analysis to the SMC comparing ulipristal acetate versus GnRH agonists, for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The time horizon for treatment was 3 months for ulipristal acetate and 3.5 months for the GnRH agonists. The economic analysis compared the total costs per patient for ulipristal acetate versus the GnRH agonist comparators, including resource costs, medicine administration, follow-up and potential adverse events. Equivalent patient outcomes between once-daily ulipristal acetate 5mg and once-monthly injections of leuprorelin acetate were demonstrated. [1]

The submitting company estimated that the total cost per patient for ulipristal acetate is £619 versus £682 for GnRH agonists (goserlin), representing a saving of £63 over the 3-4 month time horizon. The use of goserlin as a price comparator adds uncertainty as leuprorelin acetate and triptorelin acetate may be used in practice. A number of sensitivity analyses were provided, illustrating a saving with ulipristal acetate in most scenarios (ranging from £5 and £120 per patient), but with two scenarios showing ulipristal acetate resulting in additional costs (from £17 and £61 per patient).

The company made the assumption that GnRH agonist injections are classed as minor surgery procedures under Directed Enhanced Services (DES) within the General Medical Services (GMS) contract.

- Assuming 0% of GP practices claim the DES fee, the total cost per patient of GnRH agonists is £580 compared to £619 for ulipristal.
- If 31% of practices are assumed to claim the DES fee, the updated base case analysis shows that the cost per patient of GnRH agonists is £611 compared to £619 for ulipristal acetate.
- If the costs of leuprorelin acetate and triptorelin acetate were used, the savings associated with ulipristal acetate would be £28 and £6 respectively.

While there is some uncertainty surrounding the uptake of the DES fee, on balance, the economic case was considered demonstrated.

Intermittent Use - SMC Cost Effectiveness Review

Ulipristal's manufacturer submitted a cost-utility analysis to the SMC, comparing ulipristal with invasive procedures for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. [7] The analysis focused on the use of ulipristal as a second-line treatment in patients who are unsuitable for, or have failed to respond to, all available first-line pharmacological treatments. The economic analysis was conducted separately for three subgroups (peri-menopausal, fertility, and comorbidity groups) as the time horizon and comparators differed for each group. The model structure was similar to a published model used in National Institute for Health and Care Excellence (NICE) guidance on UAE for the treatment of uterine fibroids. [12] A decision tree structure was used for the short term phase (1 year), a Markov model was used to evaluate the treatments over the longer term.

In the ulipristal arm, after the first 4 courses of ulipristal treatment, patients were classified as treatment successes or treatment failures. Patients who did not respond to treatment were assumed to receive invasive procedures and patients in the 'no additional procedure' health state had a risk of failure. The short-term models for hysterectomy, UAE and myomectomy included factors such as treatment failure and adverse events. In the Markov phase of the model, the same structure is used for all treatments and captured patients receiving additional procedures.

The clinical evidence for the ulipristal arm of the short-term model was taken from the PEARL IV study. For the comparator treatments, the majority of data were taken from a separate published open-label study comparing UAE and surgery (reference source not stated). For the ulipristal arm of the model, the longer term efficacy of treatment in terms of the probability of requiring invasive procedures was based on the average rate of invasive procedures over the last 3 cycles of ulipristal treatment in the PEARL IV study. For the comparator arms, the probability of requiring a recurring procedure after 1 year was based on the rate used in the NICE guidance on UAE. The drug acquisition cost of ulipristal was included in the ulipristal arm, and for the comparator arm, a short-term course of ulipristal or GnRH was included in the pre-operative setting. Costs of procedures complications were included in the analysis. The cost of an ultrasound and follow-up annual consultant appointment was included in line with the SPC.

Group	Cost	QALY vs comparator	ICER	Notes
Peri-menopausal group	-£534	-0.0136	£39,411	ulipristal is cost-effective vs invasive procedures Not cost effective when the cost of hysterectomy reduced by 20% or when the comparator was UAE
Fertility group	-£2,646	-0.0110	£240,608	ulipristal is cost-effective vs invasive procedures Not cost-effective when the time horizon increased to 4 years
Comorbidity group	£5,511	0.3767	£14,631	Costs compared to no treatment ICER increasing to £22k when a 1 year time horizon used

The following limitations were noted:

- The use of data from the secondary endpoint instead of the primary endpoint of the proportion of patients in amenorrhoea after 4 treatment courses may overestimate the treatment effect.
- The time horizon may not be sufficient in the fertility group analysis.
- The comparator of no treatment was not included in the analysis.

Despite these limitations, the economic was considered demonstrated.

Intermittent Use - Canadian Cost Effectiveness Review

A Canadian cost-utility analysis of incorporating ulipristal for the management of symptomatic uterine fibroids was published in 2015. [19] A probabilistic decision tree was used to estimate the expected costs and quality-adjusted life years (QALYs) of two medical treatments for symptomatic uterine fibroids: ulipristal (5 mg orally daily) compared to leuprolide (3.75 mg intramuscular monthly).

An important caveat to this review was the estimated costs of treatment: the Canadian monthly cost of leuprolide (3.75 mg intramuscular) was \$347.18 (£186.54) and of ulipristal (5 mg orally) was \$343.80 (£184.72).^b [20]

The actual UK cost for leuprorelin acetate (INN^c used in the UK for leuprolide acetate^d) is £75.24 and ulipristal is £114.13. [9] Under the base-case, the expected costs for ulipristal and leuprolide were \$1,273 and \$1,366 (equivalent to £681.56 and £731.35) while the expected QALYs were 0.177 and 0.165 respectively. Ulipristal was the dominant strategy in managing women suffering from moderate-to-severe symptoms of uterine fibroids as, on average, it led to a cost saving of \$92 (£49.26) and an incremental gain of 0.012 QALYs per patient over a 3-month period.

The results remained robust to the removal of utility increments/decrements with ulipristal being the dominant strategy. Another conservative assumption tested was the impact of medical visits associated with each injection. If patients on leuprolide had no further billed medical visits except for their initial consult, the leuprolide strategy was found to be less costly (\$1,263 versus \$1,274) equivalent to £676.21 versus £682.10. As the QALYs remained unchanged (0.165 QALYs versus 0.177 QALYs), the Incremental Cost Utility Ratio for ulipristal became \$1,015.65/QALY (equivalent to £543.78/QALY) and, as the willingness-to-pay threshold rose, the probability that ulipristal was cost-effective increased.

Additional Cost Effectiveness Review

A 2016 publication evaluated the Italian pharmacoeconomic profile of repeated-intermittent (from 4 to 10 cycles) use of ulipristal acetate 5 mg in comparison with the use of ulipristal acetate 5 mg before surgery (2 cycles) for the management of symptomatic uterine fibroids. [21] The pharmacoeconomic analysis was performed in two steps: 1) estimating an incremental cost-effectiveness ratio (ICER); 2) assuming a nationwide prediction of future expenditure in the Italian scenario. Effectiveness data were derived from the randomized-controlled trial, whilst quality of life and costs data were retrieved from the published literature.

In comparison with the use of ulipristal 5 mg before surgery, the values of ICER per patient were the following: 1) €20,600 (£16,409) (ulipristal 5 mg 4 cycles); 2) €26,884 (£21,413) (ulipristal 5mg 6 cycles); 3) €30,244 (£24,090) (ulipristal 5 mg 8 cycles); 4) €31,906 (£25,414) (ulipristal 5 mg 10 cycles). In comparison with the use of ulipristal 5 mg before surgery plus subsequent surgery, the saving per patient for the National Healthcare System by adding repeated-intermittent use of ulipristal 5 mg were the following: 1) €26 million (£20.71 million) (ulipristal 5 mg 4 cycles); 2) €17.6 million (£14.02 million) (ulipristal 5mg 6 cycles); 3) €8.9 million (£7.09 million) (ulipristal 5 mg 8 cycles); 4) €0.2 million (£0.16 million) (ulipristal 5 mg 10 cycles). [22] For context, the Italian and English plus Welsh populations are similar in size. [23]

This evaluation concludes: although the data are encouraging, more data are needed regarding the benefits and risks of long-term treatment with ulipristal. [21]

^b An additional 8% pharmacy mark-up was applied to the Canadian drug prices alongside a pharmacist's dispensing fee.

^c international nonproprietary name

^d United States Adopted Name (USAN)

Relevant Guidance

NICE

NICE Clinical Guideline [CG44] Heavy menstrual bleeding: assessment and management [13]

NICE Technology Appraisal [TA78] Fluid-filled thermal balloon and microwave endometrial ablation techniques for heavy menstrual bleeding [24]

NICE interventional procedure guidance [IPG157] Endometrial cryotherapy for menorrhagia [25]

NICE interventional procedure guidance [IPG47] Photodynamic endometrial ablation [26]

NICE interventional procedure guidance [IPG522] Hysteroscopic morcellation of uterine leiomyomas (fibroids) [27]

NICE interventional procedure guidance [IPG473] Uterine artery embolisation for treating adenomyosis [28]

NICE interventional procedure guidance [IPG413] Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids [29]

NICE interventional procedure guidance [IPG367] Uterine artery embolisation for fibroids [30]

NICE interventional procedure guidance [IPG30] Magnetic resonance (MR) image-guided percutaneous laser ablation of uterine fibroids [31]

NICE interventional procedure guidance [IPG23] Laparoscopic laser myomectomy [32]

NICE interventional procedure guidance [IPG239] Laparoscopic techniques for hysterectomy [33]

SMC, AWMSG and EMAS

SMC advice 834/13: ulipristal acetate (Esmya) for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age [1]

SMC advice 1128/16: ulipristal acetate (Esmya) for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age [7]

All Wales Medicines Strategy Group Advice No:1913, Reference No.1575 ulipristal acetate (Esmya®) [14]

European Menopause and Andropause Society (EMAS) position statement on the management of uterine fibroids [2]

Strengths and Limitations of the Evidence

Strengths

- The SMC have approved ulipristal in both the pre-surgical [1] and intermittent use [7] settings
- The AWMSG have approved ulipristal in the pre-surgical setting [14] and have published a positive Preliminary Appraisal Recommendation in the intermittent use setting [16]
- Evidence for ulipristal in both the pre-surgical and intermittent settings is from the PEARL series of studies, submitted by the drug's manufacturer to gain regulatory approval for which commentary is available in the EMEA's EPAR documents. [4] [10] The licensed indication for ulipristal has followed a clear clinical study programme, which has enabled a accessible, incremental extension of the drug's license
- The PEARL studies are all of a reasonable size and power to demonstrate their primary

endpoints.

- In the pre-surgery setting, treatment groups were as follows:
 - **PEARL I** – ulipristal 5mg or 10mg vs placebo for 13 weeks
 - **PEARL II** – ulipristal 5mg or 10mg plus placebo vs placebo plus leuprorelin 3.75mg for 13 weeks
- **PEARL II** therefore provided a head to head comparison of ulipristal vs leuprorelin

Limitations

- In the intermittent use setting, treatment groups were as follows:
 - **PEARL III** – ulipristal 10mg daily for 3 months, followed by norethisterone or placebo daily for 10 days
 - **PEARL IV** – ulipristal 5mg vs ulipristal 10mg daily for 12 weeks (3 courses) then a 3-month drug-free period following the fourth treatment course
- In the intermittent treatment setting, ulipristal was only compared with a different, unlicensed dose of ulipristal. There are no head to head trials with active comparators in the intermittent treatment setting
- The rationale for lack of placebo in the **PEARL IV** study was accepted by the EMEA as previous short term studies had shown that that ulipristal was superior to placebo in reducing menstrual bleeding and fibroid size (**PEARL I** study) [15] and was non-inferior to monthly injections of leuprorelin acetate for controlling uterine bleeding (**PEARL II** study). [3] A placebo arm was therefore considered unethical in the **PEARL IV** study. [4]
- Unlicensed doses of ulipristal were used in some of the PEARL studies, limiting the applicability of some study findings to real world prescribing

Prescribing and risk management issues:

Ulipristal should only be prescribed by specialists (e.g. gynaecologists) in the secondary care setting. The drug needs specialist outpatient prescribing as the treatment of fibroids is specialist in nature with considerations for surgery, scans, blood tests and histology requiring specialist input and control. There are specific dosing instructions which are not appropriate for prescribing via the FP10 route.

Commissioning Considerations

Comparative Unit Costs

Drug	Example regimen	Pack cost	Cost per patient per course
Ulipristal (Esmya 5mg)	5mg orally daily. Each course can last up to 3 months - repeated intermittent treatment has been studied up to 4 intermittent courses. Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion - it is reasonable to set a maximum use of around 3 courses of 3 months in the first year.	£114.13	Year 1 £1027.17 Year 2 £342.39
Ulipristal (Esmya 5mg)	5mg orally daily. Equivalent of 6 months treatment	£114.13	£684.78
Goserelin (Zoladex 3.6mg)	3.6mg by subcutaneous injection every 28 days for 6 months maximum	£65.00	£390.00
Leuprorelin (Prostap SR DCS 3.75mg)	3.75mg by subcutaneous or intramuscular injection every 28 days for 6 months maximum	£75.24	£451.44
Triptorelin (Decapeptyl SR 3mg)	3mg by intramuscular injection every 28 days 6 months maximum	£69.00	£414.00
Triptorelin (Gonapeptyl Depot 3.75mg)	3.75mg by subcutaneous or intramuscular injection every 28 days 6 months maximum	£81.69	£490.14

Costs based on BNF prices April 2016, excluding administration costs and VAT. [9] Table does not imply therapeutic equivalence of drugs or doses.

Associated additional costs or available discounts:

Ulipristal should not be used as a contraceptive and a non-hormonal contraceptive method is recommended during treatment. Concomitant use of ulipristal and a hormonal contraceptive has the potential to reduce the efficacy of both drugs. [8] Annual ultrasound is recommended to monitor endometrial thickening. [8]

Productivity, service delivery, implementation:

Ulipristal is an oral tablet. Other treatments used in the pre-surgical setting such as the GnRH analogues are depot type injections. A switch to ulipristal will remove the need for healthcare professional administration.

In the intermittent setting ulipristal may provide an attractive treatment alternative to the peri-menopausal group, enabling patients to manage the symptoms of uterine fibroids until menopause (at which point it is likely that symptoms will subside naturally) and thus avoiding major surgery and the complications associated with surgical procedures.

Anticipated Patient Numbers and Budget Impact

Pre-surgery Setting

For the SMC's review of ulipristal the drug's manufacturer estimated the population eligible for treatment with ulipristal in the pre-surgery setting to be 711 in year 1 rising to 771 in year 5, with an estimated uptake rate of 9% in year 1 and 43% in year 5. [1]

The population of Scotland has been estimated to be 5,347,600. [23] Using the figures, above, the equivalent incidence of patients in the pre-surgical setting can be calculated is 14.4 per 100,000 population. At a 9% uptake in year 1, 1.296 patients per 100,000 population will be eligible for treatment, rising to 6.192 per 100,000 population in year 5. Per 100,000 population the annual costs of ulipristal are estimated to be £887.47 in year 1 rising to £4,240.16 in year 5.

For **Lancashire**, with an estimated population of around 1.5 million, the estimated **acquisition costs** for ulipristal in the pre-surgery setting will be as follows:

Year 1: £13,312

Year 5: £63,602

The SMC analysis suggest that a course of treatment with ulipristal acetate 5 mg is estimated to achieve a cost saving of £59.49 per patient when compared to the cheapest GnRHa comparator, goserelin acetate. [14] A per 100,000 population saving of £77.10 may be achieved in year 1, rising to £368.36 in year 5.

For **Lancashire**, the estimated **savings** will be as follows:

Year 1: £1,157

Year 5: £5,525

Intermittent Use Setting

For the SMC's review of ulipristal the drug's manufacturer estimated there would be 829 patients eligible for treatment in the intermittent use setting in year 1, rising to 2,105 in year 5. The update rate was estimated to be 29% in year 1 (240 patients) and 60% (1,263 patients) in year 5. [7].

Using the figures, above, the equivalent incidence of patients in the intermittent use setting can be calculated as 15.5 per 100,000 population in year 1 rising to 39.3 per 100,000 population in year 5. Factoring in the uptake figures, the number of patients estimated to be treated in the intermittent setting are 4.495 per 100,000 in year 1, rising to 23.58 per 100,000 by year 5. This equates to a budget impact of £3,078.09 per 100,000 in year 1 rising to £16,147.11 per 100,000 by year 5 using 6 month's treatment per patient.

For **Lancashire**, with an estimated population of around 1.5 million, the estimated **acquisition costs** for ulipristal in the intermittent use setting will be as follows:

Year 1: £46,171

Year 5: £242,207

Innovation, need, equity:

In addition to ulipristal, GnRH agonists (goserelin, leuprorelin and triptorelin) are licensed for the pre-operative management of uterine fibroids.

Ulipristal is the only treatment licensed for intermittent use in uterine fibroids.

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