Ulipristal acetate: new oral treatment for uterine fibroids

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KEY POINTS

- ulipristal acetate (Esmya) is a progesterone receptor modulator
- licensed for preoperative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age; duration is limited to 3 months
- available as a 5mg tablet; recommended dose is 1 tablet taken orally daily for up to 3 months; 28=£114.13
- first selective progesterone receptor modulator licensed for the preoperative treatment of uterine fibroids
- in 2 phase 3 trials fibroid volume was reduced by 20–35 per cent (5mg daily)
- sustained fibroid volume reduction seen for 6 months post-treatment of 3 months
- rapid control of excessive bleeding seen in both trials with ulipristal acetate
- ulipristal acetate could have in role in the first-line treatment of fibroids over 3cm; patients who will derive most benefit will be those with heavy bleeding, infertility due to fibroids and in the perimenopausal age group

Ulipristal acetate is the first progesterone receptor modulator licensed for the preoperative treatment of uterine fibroids. Our New products review presents the clinical data relating to its efficacy and adverse events and considers its place in medical management of uterine fibroids.

Fibroids are the most common benign tumours in women of reproductive age. Uterine fibroids are also known as leiomyomata, myoma and leiomyoma. They originate from uterine smooth muscle cells and in some cases from the blood vessels of the uterine smooth muscles. They may be solitary or multiple and the symptoms depend on their location, size and concomitant degenerative changes.[1,2]

Common symptoms include excessive menstrual bleeding due to vascular alterations. Other effects of the myomas may be an obstruction that contributes towards the excessive bleeding.[3,4] The increased size of the uterine cavity and the increased surface area also contribute towards this excessive bleeding. Many patients therefore present with anaemia, which complicates surgical treatment options.

Other common symptoms are increased abdominal girth and pressure symptoms caused by the size and position of the myoma. Pressure symptoms could include increased frequency of micturition, urinary tract outflow obstruction and ureter compression.[5] Pain is usually caused by torsion of a pedunculated myoma or due to cervical dilatation as a result of a submucous myoma. Infertility is thought to be caused by submucous myomas where the endometrial cavity has caused a drastic distortion, or by an enlarged endometrial cavity that may be seen to interfere with the normal implantation of ova or transportation of the sperm. Intramural myomas may cause obstruction of the ostium of the fallopian tubes that may lead to decreased pregnancy rates.

In 2009/10 there were about 74 500 inpatient interventions for uterine fibroids in NHS hospitals in England, which places a large financial burden on the NHS and also has a significant impact on the quality of life for the patient.

The technology

Ulipristal acetate (Esmya) is a selective progesterone receptor

modulator licensed for the preoperative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to three months.[6]

Ulipristal acetate has a tissue-specific partial progesterone antagonist effect, acting on progesterone receptors in the endometrium and myometrium preventing further stimulation of fibroid growth. Ulipristal acetate also exerts a direct action on fibroids, reducing their size through inhibition of cell proliferation and induction of apoptosis.

On a daily recommended dose of 5mg, it suppresses follicle stimulating hormone (FSH) levels. However, serum oestradiol levels remain in the mid-follicular range in a majority of patients, and the better side-effect profile would be the result of these maintained oestradiol levels. Ulipristal acetate does not affect serum levels of thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) or prolactin over three months of treatment.[6]

The efficacy of ulipristal acetate may be affected by CYP3A4 inhibitors, and co-administration of moderate or potent CYP3A4 inhibitors is not recommended.[6]

Clinical trials

The efficacy of fixed doses of ulipristal acetate 5mg and 10mg once daily was evaluated in two phase 3 randomised, double-blind, 13-week studies recruiting patients with very heavy menstrual bleeding associated with uterine fibroids.

Study 1 (Pearl I[7]) was double blind and placebo controlled. Patients were required to be anaemic at study entry (Hb <10.2g per dl) and all patients were to receive oral iron 80mg Fe^{++} in addition to the study drug.

Study 2 (Pearl II[8]) contained the active comparator leuprorelin (Prostap) 3.75mg given once per month by intramuscular injection. A double-dummy method was used to maintain the blind.

In both studies menstrual blood loss was assessed using the Pictorial Bleeding Assessment Chart (PBAC). A PBAC >100 within the first eight days of menses is considered to represent excessive menstrual blood loss.

In Pearl I, a statistically significant difference was observed in the reduction in menstrual blood loss in favour of the patients treated with ulipristal acetate compared to placebo, resulting in faster and more efficient correction of anaemia than iron alone. Likewise, patients treated with ulipristal acetate had a greater

Parameter	Study 1 – Pearl I			Study 2 – Pearl II		
	Placebo n=48	Ulipristal acetate 5mg/day n=95	Ulipristal acetate 10mg/day n=94	Leuprorelin 3.75mg/ month n=93	Ulipristal acetate 5mg/day n=95	Ulipristal acetate 10mg/day n=95
Menstrual bleeding						
median PBAC at baseline	376	386	330	297	286	271
median change at week 13	-59	**-329**	**-326**	-274	-268	-268
Patients in amenorrhea at week 13	3 (6.3%)	**69 (73.4%)**[a]	**76 (81.7%)**[b]	74 (80.4%)	70 (75.3%)	85 (89.5%)
Patients whose menstrual bleeding became normal (PBAC <75) at week 13	9 (18.8%)	**86 (91.5%)**[a]	**86 (92.5%)**[a]	82 (89.1%)	84 (90.3%)	93 (97.9%)
Median change in myoma volume from baseline to week 13	+3.0%	**-21.2%**[c]	**-12.3%**[d]	-53.5%	-35.6%	-42.1%

In Study 1, change from baseline in total myoma volume was measured by MRI; in Study 2, change in the volume of the 3 largest myomas was measured by ultrasound; bold values indicate that there was a significant difference in the comparisons between ulipristal acetate and the control (in favour of ulipristal acetate); *p* values: a=<0.001, b=0.037, c=<0.002, d=<0.006; PBAC = Pictorial Bleeding Assessment Chart

Table 1. Results of primary and selected secondary efficacy assessments in phase 3 studies

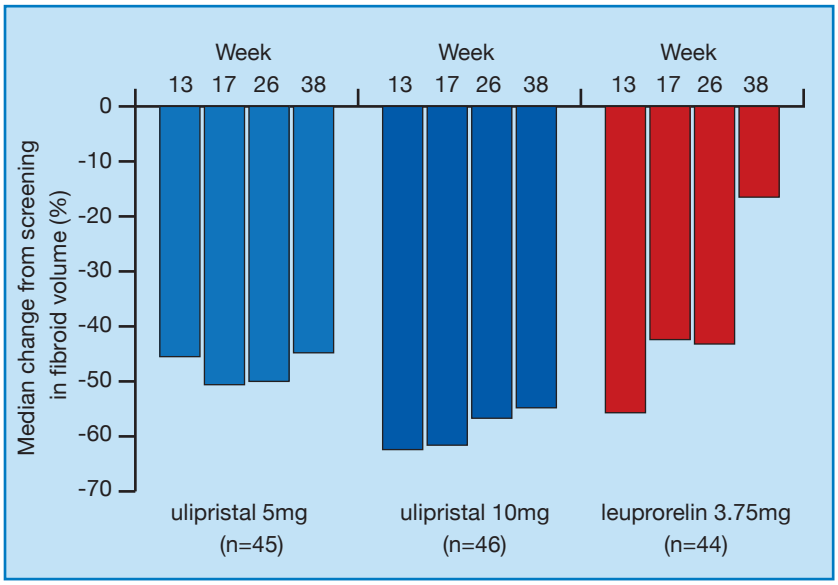

Figure 1. Effects on fibroid volume six months after stopping treatment (PEARL II; n=135 patients who did not have surgery); the 10mg ulipristal dose is currently unlicensed

reduction in myoma size, as assessed by magnetic resonance imaging (MRI, see Table 1).

In Pearl II, the reduction in menstrual blood loss was comparable for patients treated with ulipristal acetate and the gonadotrophin-releasing hormone (GnRH) analogue leuprorelin (see Table 1). Most patients treated with ulipristal acetate stopped bleeding (amenorrhoea) within the first week of treatment compared with four weeks in patients taking leuprorelin.

The size of the three largest myomas was assessed by ultrasound at the end of treatment (week 13) and for another 25 weeks without treatment in patients who did not have a hysterectomy or myomectomy performed. Myoma size reduction was generally maintained during this follow-up period in patients originally treated with ulipristal acetate but some regrowth occurred in patients treated with leuprorelin (see Figure 1).

Adverse effects

In Pearl I, the rate of adverse events was not significantly different to placebo in any of the arms. The most common adverse events were headache and breast tenderness. The rate of hot flushes was low (under 3 per cent) in all groups. There was no significant difference among the groups in the incidence of abnormal liver function tests or mean endometrial thickness. A minority of patients in the treatment arm had endometrial thickness greater than 16mm at the end of treatment (week 13); this had reversed in all cases by week 26 or 38.

In Pearl II, moderate to severe hot flushes occurred in four times as many patients treated with leuprorelin. The oestradiol levels were 64pg per ml (234pmol per litre) in the 5mg ulipristal acetate treatment arm and 60.5pg per ml (222pmol per litre) in the 10mg arm, which are in the mid-follicular range. However, the comparator arm of leuprorelin showed oestradiol levels dropping to postmenopausal levels of 25pg per ml (92pmol per litre). Apart from these two adverse events, the other events did not show any statistical significance.

Similar to Pearl I, at the end of treatment (week 13) mean endometrial thickness was 9.4mm in the 5mg treatment arm and 10.7mm in the 10mg arm. Endometrial biopsy showed no findings of clinical concern. Nonphysiological endometrial changes were seen in a majority of the treatment patients that

had returned to normal levels at week 38.

These nonphysiological changes fall under a new morphological class of PRM (progesterone receptor modulator)-associated endometrial changes (PAEC). The manufacturer, under instruction from the European regulators, has developed an educational plan to contact pathologists and gynaecologists to inform them of PAEC changes and that they return to normal after cessation of treatment and occurrence of menstruation.

Place in therapy

Ulipristal acetate is a new agent in the medical management of uterine fibroids in the presurgical arena. The NICE clinical guideline for heavy menstrual bleeding[9] recommends the use of pharmaceutical treatment (first line, second line, *etc*) if the fibroid size is less than 3cm.

However, if the fibroid is more than 3cm and is accompanied by a significant symptom, the treatment options are limited to GnRH analogues and surgery. GnRH analogues have a marked side-effect profile with an initial 'flare response' that can actually increase the size of the fibroid as well as triggering the hot flushes associated with a chemical menopause.

Ulipristal acetate would have a role in the first-line treatment of fibroids more than 3cm as its use would avoid a flare and menopausal side-effects and provide rapid relief of menstrual loss. Patients who would benefit the most would be those with heavy bleeding who need quick restoration of their menstrual periods, those whose infertility is due to fibroids and patients who are in the perimenopausal age group.

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Declaration of interests

Dr McVeigh was a member of the PregLem European Advisory Board during the clinical studies on ulipristal acetate, for which he received an honorarium.

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