General Commissioning Policy

Treatment	Ulipristal acetate (Esmya▼; Preglem UK)
For the treatment of	Pre-operative treatment of severe symptoms of uterine fibroids in adult women of reproductive age.
Background	Ulipristal will be the first orally administered option for reducing excessive bleeding and uterine fibroid size prior to surgery, compared with GnRH analogues which need to be given subcutaneously. This will give patients a choice which they may find preferable. Oral therapy will reduce the time and cost of doctors and nurses who currently administer the subcutaneous treatments.
Commissioning position	Ulipristal is not routinely commissioned for symptoms of uterine fibroids
Effective from	September 2012
Summary of evidence / rationale	**London New Drugs Group: Ulipristal acetate (Esmya); May 2012.** http://www.medicinesresources.nhs.uk/upload/Ulipristal_May12b.pdf Uterine fibroids are the most common benign, hormone sensitive tumours in women of reproductive age, occurring in 20-40%. Many go undiagnosed but 20-50% will require clinical intervention. NSAIDs are used to reduce menstrual blood loss and dysmenorrhoea by antagonizing prostaglandins which cause the uterus to contract, leading to pain. Tranexamic acid and danazol reduce the heavy bleeding. Danazol can also lead to fibroid shrinkage but is limited due to side effects such as acne and weight gain. GnRH agonists is the main treatment option used at present which reduce hormonal stimulation of fibroids that results in a reduction in the size by 25-50% within 3 months, but the fibroids regrow to their former size within 3-6 months of stopping treatment. Surgery is indicated when the uterus is greatly enlarged, pressure symptoms are present, medical management cannot control the symptoms and fertility is an issue. 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. The only concern regards to the latter there is always the risk that the fibroids may reappear and therefore require further surgery. Ulipristal is a selective progesterone receptor modulator which acts on progesterone receptors in muometrial and endometrial tissue and depriving uterine fibroids of growth stimulation due to progesterone treatment is 5mg daily for up to 3 months only. There is no data for longer than 3 months or repeated courses. No dose adjustment is required in patients with mild/moderate renal impairment or mild hepatic impairment. It should not be used in patients with uterine, cervical, ovarian or breast cancer, in those with genital bleeding of unknown cause.

Notes

1. This Policy will be reviewed in the light of new evidence, or guidance from NICE.
2. General Commissioning Policies are agreed by the Planning and Commissioning Committee on behalf of NHS Hull CCG.

Points for consideration:

- There are only efficacy data for the use of ulipristal for up to 3 months. [Note that the GnRH agonist goserelin is only licensed for 3 months and leuprorelin and triptorelin are licensed for up to 6 months of treatment for reducing uterine fibroids].
- Reduction in fibroid volume was maintained for a longer period of time with ulipristal than with leuprorelin in patients who did not undergo surgery.
- There are no data on the use of ulipristal following a GnRH agonist, or followed by a GnRH agonist.
- The PEARL studies did not assess surgical outcomes following ulipristal therapy.

NICE Clinical guideline 44: Heavy menstrual bleeding. January 2007
http://www.nice.org.uk/nicemedia/live/11002/30403/30403.pdf
NICE guidance recommends that GnRH agonists are used 3-4 months prior to a hysterectomy or myomectomy when fibroids are >3cm and are having a significant impact on quality of life.

Clinical Trials

Ulipristal acetate versus placebo for fibroid treatment before surgery (PEARL I)
Donnez J et al
N Engl J med, 2012 Feb 2; 365 (5): 409-20
The main aim of this study was to assess the efficacy and safety of ulipristal 5mg and 10mg daily on uterine bleeding and fibroid volume in 242 women with symptomatic fibroids who were planning to undergo surgery. Inclusion criteria were women aged 18-50 years with a score on the pictorial blood-loss assessment chart (PBAC) higher than 100 during days 1-8 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 BMI of 18-40, also fibroid-related anaeamia (Hb < 10.2g/dl).

Exclusion criteria included: 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, previous or current treatment for fibroids with a GnRH agonist, treatment with agents that affect CYP3A4 or those taking progestins, aspirin, mefenamic acid, anticoagulants, antifibrinolytic drugs or systemic glucocorticoids.

Patients were randomly assigned to oral ulipristal at a dose of 5mg per day (n=96) or 10mg per day (n=98) or placebo (n=48) for 13 weeks. All patients received iron supplementation. The coprimary endpoints were control of uterine bleeding (PBAC score of <75) and a reduction of fibroid volume at week 13, after which patients could undergo surgery.

At 13 weeks, uterine bleeding was controlled in 91% of the women receiving 5mg of ulpristal, 92% of those on 10mg and 19% of those on placebo (p<0.001 for the comparison of each dose of ulpristal with placebo). The rates of

	amenorrhoea were 73%, 82% and 6% respectively. The median changes in total fibroid volume were -21%, -12% and +3% (p=0.002 for comparison of 5mg with placebo, and p=0.006 for the comparison of 10mg with placebo). The rate of adverse events did not differ significantly between the three groups. The most common adverse events in the ulpristal group were headache and pain, discomfort or tenderness in the breast but these events did not occur significantly greater extent than in the placebo group. Approximately half the patients in each group had fibroid surgery after completing the study. Note the study did not assess treatment-related differences in surgical outcomes and the 5mg dose is the licensed dose in the UK. **Ulipristal acetate versus leuprolide acetate for uterine fibroids (Pearl II). Donnez J et al.** **N Engl J Med, 2012 Feb 2; 366 (5): 421-32.** The aim of this study was to assess the efficacy and side effects of ulpristal versus leuprolide acetate (Leuprorelin) for treating symptomatic uterine fibroids prior to surgery. It was a double blind noninferiority trial, we randomly assigned 307 patients with symptomatic fibroids and excessive uterine bleeding to receive 3 months of daily therapy with oral ulipristal (5mg (n=98) or 10mg (n=104)) or once-monthly IM injections of leuprolide (dose of 3.75mg; n=101). The primary endpoint was the proportion of patients with controlled bleeding at week 13, with a prespecified noninferiority margin of -20%.Uterine bleeding was controlled in 90% of patients receiving 5mg ulpristal, in 98% of patients receiving 10mg and in 89% of those receiving leuprolide, for differences (as compared to leuprolide) of 1.2% points (95% CI, 0.4 to 18.3) for 5mg dose and 8.8% points (95% CI, 0.4 to 18.3) for 10mg dose. Median % change in total fibroid volume was -36 for the 5mg dose, -42 for the 10mg dose and -53 in the leuprorelin group. Median times to amenorrhoea were 7 days for patients receiving 5mg of ulpristal, 5 days for those receiving 10mg ulipristal and 21 days for those receiving leuprolide. Moderate to severe hot flushes were reported for 11% of patients receiving 5mg ulpristal, 10% of those on 10mg and for 40% of those receiving leuprolide acetate 9p<0.001 for each dose of ulpristal vs. leuprolide). In summary, the efficacy of ulipristal to reduce bleeding associated with fibroids was non-inferior to that of leuprorelin. Once again surgical outcomes were not assessed as one of the study outcomes.
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Policy to be reviewed by	September 2014
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