ulipristal acetate, 5mg, tablet (Esmya®) SMC No. (834/13)
Gedeon Richter UK Ltd.

11 January 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

*ulipristal acetate (Esmya®)* is accepted for use within NHS Scotland.

**Indication under review:** Pre-operative treatment of moderate-to-severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to three months.

Ulipristal was superior to placebo and non-inferior to a gonadotrophin releasing hormone (GnRH) agonist for reducing uterine bleeding in pre-operative women with uterine fibroids and excessive bleeding.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**
**Indication**
Pre-operative treatment of moderate-to-severe symptoms of uterine fibroids in adult women of reproductive age. The duration of treatment is limited to three months.

**Dosing Information**
5mg orally once daily for up to three months. Treatment should be started during the first week of a menstrual cycle.

There are no data available on treatment with a duration longer than three months or on repeat courses of treatment, therefore, treatment duration should not exceed three months.

**Product availability date**
02 April 2012

**Summary of evidence on comparative efficacy**

Uterine fibroids are common, hormone-sensitive, benign smooth muscle tumours. Symptoms include heavy uterine bleeding, anaemia, abdominal pressure and pain, urinary frequency and infertility. Symptomatic fibroids are treated with surgery (hysterectomy, myomectomy, uterine artery embolisation or endometrial ablation). Gonadotrophin-releasing hormone (GnRH) agonists, administered via intramuscular or subcutaneous injection are licensed for the pre-operative treatment of symptomatic uterine fibroids. They reduce fibroid-related bleeding and abdominal symptoms. 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.

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. Ulipristal 5mg and 10mg doses were studied; however, the results for ulipristal 5mg only are presented as this is the licensed dose.

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 and a body-mass index between 18 and 40kg/m$^2$. The women had a myomatous uterus with a size equivalent to that of a uterus at 16 weeks or less of gestation, one or more fibroids $\geq$3cm 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. Patients received iron supplementation at the discretion of the treating physician. After week 13, patients could undergo surgery according to the clinical judgement of the investigator.

The primary efficacy endpoint, measured in the per-protocol population, was the proportion of patients with control of uterine bleeding at week 13, defined as a PBAC score (summed over the
preceding 28 day period) of less than 75. 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 (PBAC score ≤2) was induced more rapidly in ulipristal-treated patients compared with those receiving leuprorelin: median time to amenorrhoea was 7 days and 21 days, respectively.

Both study groups had a similar improvement in pain scores measured using the short-form McGill Pain Questionnaire: the median change from baseline (interquartile range) was -5.0 (-11.0 to -2.0) and -5.5 (-14.5 to -2.0) in the ulipristal 5mg and leuprorelin groups respectively. Quality of life was measured using the uterine fibroid symptom and quality of life questionnaire. The mean (+ standard deviation) change from baseline in the health-related quality of life score was 24 (+27) and 23 (+28), respectively.

PEARL I was a 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 (haemoglobin ≤10.2g/dL without macrocytosis). Patients were randomised in a 2:2:1 ratio, and stratified, according to haematocrit level at screening and race, to receive ulipristal 5mg, 10mg or placebo daily, started during the first four days of menstruation and continued until week 13. All patients received 80mg of iron supplementation (256.3mg of ferrous sulphate) once daily during the active treatment phase. After week 13, patients could undergo surgery according to the clinical judgement of the investigator.

The co-primary efficacy endpoints, measured in the modified intention to treat population, 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 (PBAC ≤2 at week 9 to 12) was achieved in significantly more patients receiving ulipristal 5mg than receiving placebo (73% [69/94] versus 6% [3/48], *p*<0.001). Change in mean (+ 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.

Pain was also assessed using the short-form McGill Pain Questionnaire. The median change from baseline to week 13 (interquartile range) was -5.0 (-8.0 to -2.0) in the ulipristal 5mg group and -2.5 (-6.3 to 1.0) in the placebo group, *p*=0.10. Quality of life was measured using a questionnaire assessing discomfort associated with uterine fibroids; scores can range from 0 to 28 with higher scores indicating more discomfort. 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) respectively, *p*=0.001.
Summary of evidence on comparative safety

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.

Summary of clinical effectiveness issues

Uterine fibroids are estimated to occur in 20% to 40% of women of reproductive age. Fibroids are often asymptomatic, however, when symptomatic they can cause frequent disabling symptoms, the most troublesome of which is heavy uterine bleeding. The current treatment for symptomatic fibroids is surgery. GnRH agonists may be given for three to four months before surgery when the uterine fibroids cause an enlarged or distorted uterus. They are administered by monthly intramuscular or subcutaneous injections. Ulipristal is the first oral preparation licensed for the pre-operative treatment of moderate-to-severe symptoms of uterine fibroids.

In patients with symptomatic uterine fibroids, ulipristal (5mg oral daily) was superior to placebo and non-inferior to the GnRH agonist leuprorelin (3.75mg intramuscular injection monthly) in PEARL I and PEARL II respectively, for the primary endpoint of reduction in uterine bleeding at three months, calculated using PBAC. This is an indirect measure of menstrual bleeding that has been validated against alkaline haematin. However, the National Institute for Health and Clinical Excellence (NICE) considers the evidence for the use of PBAC to be contradictory, and there are no data available to support use in routine practice.

Ulipristal is only licensed for three months of treatment; there are limited efficacy and safety data beyond three months. Goserelin is also licensed for three months, leuprorelin is usually given for three to four months to a maximum of six months and triptorelin is licensed as a treatment for a minimum of three months and a maximum of six months, for this indication.

SMC clinical experts advise that all GnRH agonists are used in Scotland for this indication. There are no clinical data comparing triptorelin or goserelin to ulipristal; however, GnRH agonists are considered equivalent for this indication. The NICE clinical guideline 44: Heavy Menstrual Bleeding states that a GnRH agonist can be considered in all patients prior to surgery and is recommended if the uterine fibroids have caused an enlarged or distorted uterus. Some
patients require ‘add-back’ therapy with hormone replacement therapy because of the adverse effects of GnRH agonists.3

Women may prefer a daily oral tablet to a monthly intramuscular or subcutaneous injection. 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. The introduction of ulipristal 5mg may have service benefits by reducing the need for monthly injections. There may be particular benefits for patients in remote and rural areas.

**Summary of comparative health economic evidence**

The submitting company presented a cost-minimisation analysis (CMA) 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.

In this economic analysis, the comparator is a class of medicines. This is appropriate on the basis that the efficacy of GnRH agonists is expected to be equivalent in clinical practice, as noted in the clinical-effectiveness section above.

The clinical evidence to support the use of a CMA came from the results of the pivotal study, where equivalent patient outcomes between once-daily ulipristal acetate 5mg and once-monthly injections of leuprorelin acetate (representative of GnRH agonists) were demonstrated.

The economic analysis compared the total costs per patient for ulipristal acetate versus the GnRH agonist comparators. Costs included medicine costs, and also the resource use costs associated with diagnosis, medicine administration, and follow-up. The analysis also included costs associated with potential adverse events.

The submitting company estimated that the total cost per patient for ulipristal acetate is £619 versus £682 for GnRH agonists, representing a saving of £63 over the 3-4 month time horizon. For the purpose of these base case calculations, the medicines acquisition cost for goserelin was used as the comparator.

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).

There was one key uncertainty with the analysis. The submitting company has assumed that GnRH agonist injections are classed as minor surgery procedures under Directed Enhanced Services (DES) within the General Medical Services (GMS) contract in Scotland. A GP practice is entitled to charge a fee for DES provided by the practice. The submitting company’s economic model assumes that each GnRH agonist injection attracts this fee. Considerable doubt has been cast on this assumption.

An additional uncertainty surrounds the choice of GnRH agonist comparator used within the base case cost calculations. The submitting company has used the cost of goserelin acetate within their calculations, although SMC clinical experts suggest that leuprorelin acetate and
triptorelin acetate may be more widely used in practice. Given the relative price of goserelin, this is a conservative assumption. To explore these uncertainties, further analyses were provided:

- Assuming 0% of GP practices claim the DES fee, the total cost per patient of GnRH agonists is £580 compared to £619 for ulipristal acetate, meaning that the additional cost of ulipristal acetate is £39.

- If 0% of GP practices claim the DES fee, then regardless of the GnRH comparator used within the cost calculations, ulipristal acetate is not cost saving. Using the costs of leuprorelin acetate and triptorelin acetate within the analysis resulted in an additional cost associated with ulipristal acetate of £4 and £25 respectively.

- The submitting company carried out some market research to provide an estimate of the percentage of GP practices which currently claim the DES fee. Based on the submitting company’s telephone survey of 141 GPs in Scotland, of 72 respondents, 22 (31%) said that they always or mostly claim the DES fee for administering GnRH agonists. 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. In this case the additional cost of ulipristal acetate is £8. Threshold analysis on the base case indicated that 39% of GP practices would need to claim the DES fee for ulipristal acetate to be the preferred treatment.

- Alongside the assumption that 31% of practices claim the DES fee, the submitting company also altered the choice of GnRH comparator within the cost calculations. 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.

**Summary of patient and public involvement**

A Patient Interest Group Submission was received from the British Fibroid Trust.

**Additional information: guidelines and protocols**

NICE published a clinical guideline in 2007: Heavy menstrual bleeding. Use of a GnRH analogue could be considered prior to surgery or when all other treatment options for uterine fibroids, including surgery or uterine artery embolisation, are contraindicated. If this treatment is to be used for more than 6 months or if adverse effects are experienced then hormone replacement therapy (HRT) ‘add-back’ therapy is recommended. Pre-treatment with a GnRH analogue for three to four months should be considered prior to a hysterectomy or myomectomy when the uterine fibroids are causing an enlarged or distorted uterus. This guideline predates the availability of ulipristal.
Additional information: comparators

GnRH agonists’ goserelin, leuprorelin and triptorelin are licensed for the pre-operative management of uterine fibroids.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
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</thead>
<tbody>
<tr>
<td>Ulipristal</td>
<td>5mg orally daily</td>
<td>342</td>
</tr>
<tr>
<td>Goserelin</td>
<td>3.6mg by subcutaneous injection every 28 days</td>
<td>195</td>
</tr>
<tr>
<td>Leuprorelin</td>
<td>3.75mg by subcutaneous or intramuscular injection every 28 days</td>
<td>226</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>3mg by intramuscular injection every 28 days</td>
<td>207</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>3.75mg by subcutaneous or intramuscular injection every 28 days</td>
<td>245</td>
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</tbody>
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Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 15/10/2012. Costs are based on a three month course of each drug, leuprorelin and triptorelin 3mg and 3.75mg may be given up to a maximum of six months at a cost of £451, £414 and £490 respectively.

Additional information: budget impact

The submitting company estimated the population eligible for treatment 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. The gross impact on the medicines budget was estimated to be £22k in year 1 and £114k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £5k in year 1 and £28k in year 5.
References

The undernoted references were supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 13 December 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.