

ulipristal acetate, 5mg, tablet (Esmya®)

SMC No. (1128/16)

Gedeon Richter (Uk) Ltd

8 January 2016

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 NHS 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: for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

A phase III study demonstrated that 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.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

For the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Dosing Information

One ulipristal acetate 5mg tablet to be taken orally once daily for treatment courses of up to three months each.

Treatments should only be initiated when menstruation has occurred:

- 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 four intermittent courses.

Product availability date

27 May 2015

Summary of evidence on comparative efficacy

Uterine fibroids are benign, monoclonal, smooth muscle, hormone-sensitive tumours which are thought to affect 20 to 40% of women during their reproductive years.^{1,2} Ulipristal acetate (hereafter referred to as ulipristal) is a selective progesterone receptor modulator with a tissue-specific, partial progesterone antagonist effect. It exerts a direct effect on the endometrium which prevents menstruation and reduces the symptoms and size of uterine fibroids. Ulipristal reduces cell proliferation and induces cell death in myoma (fibroid) cells but not in normal myometrial cells. It also acts centrally, on the hypothalamic–pituitary–ovarian axis, to inhibit or delay ovulation and it partially suppresses follicle-stimulating hormone (FSH) levels although serum oestradiol levels are maintained in most patients, thereby avoiding oestrogen deficiency and its associated symptoms.³

Ulipristal has previously been accepted by SMC for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age, limited to one treatment of three months' duration.³ The marketing authorisation has been extended to allow repeated intermittent treatment in patients who may not require surgery and there is study evidence for use of up to four intermittent courses.³ The submitting company has requested that SMC reviews 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 (normally focused on the control of heavy menstrual bleeding [HMB]). "First-line treatment" refers to all currently available pharmacological treatments.

The main evidence for this license extension comes from one pivotal phase III, double-blind, randomised, controlled study (PEARL IV) in pre-menopausal women with uterine fibroids and

HMB.^{1,2} Supportive data were also presented from a phase III open-label study (PEARL III) (which used an unlicensed dose of ulipristal) and its extension study.⁴

PEARL IV included 451 pre-menopausal women aged 18 to 50 years with body mass index ≥ 18 and ≤ 40 and FSH level ≤ 20 mIU/mL. They were required to have uterine fibroids with uterus size < 16 weeks (i.e. comparison to a uterus of 16 weeks of pregnancy), largest myoma ≥ 3 cm and ≤ 12 cm in diameter, menstrual cycle ≥ 22 and ≤ 35 days and Pictorial Bleeding Assessment Chart (PBAC) score > 100 (indicating menorrhagia) as measured during screening over the first eight days of the menstrual cycle.^{1,2}

Patients were randomised in a 1:1 ratio, stratified by site, to receive once daily oral treatment with 5mg (licensed dose) or 10mg ulipristal for four courses of 12 weeks each, separated by drug-free intervals. Treatment was initiated during the first four days of menstruation and subsequent courses started at the time of the second off-treatment menstruation. The study was fully blinded until the completion of part I (first two treatment courses) when the sponsor, statistics and data management personnel were unblinded. Investigators, monitors, pathologists and patients remained blinded until the completion of the full study (four courses).¹

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 in a diary using an eight-day PBAC at screening, when a score of > 100 was required for inclusion, and after treatment courses 1, 2 and 4. PBAC is a validated self-reporting tool for assessing menstrual blood loss and has been widely used for evaluating drugs or devices for the treatment of HMB. Patients were provided with standardised sanitary materials and recorded daily the number of tampons and towels used and the degree to which individual items were soiled with blood.² Bleeding occurring outside the timeframe described above was recorded in the diary and categorised as no bleeding, spotting, bleeding or heavy bleeding.¹ Analyses were conducted on 384 patients from the full analysis set (FAS, $n=451$) 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% confidence interval [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%; $p=0.027$).¹

There was no significant difference between treatment groups for the secondary outcome of controlled bleeding (no episodes of heavy bleeding and a maximum of eight days of bleeding in the last 56 days of all four individual treatment courses): 67% (106/158) and 72% (105/146) of evaluable patients in the 5mg and 10mg groups, respectively. The proportion of patients in the 5mg dose group with controlled bleeding after treatment course 4 (regardless of previous courses) was 73% (148/202) and in the 10mg group was 75% (144/192).¹ 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 was assessed by visual analogue scale (0mm=no pain and 100mm=worst possible pain) recorded in a diary. Reduction in pain was similar in both groups: from a baseline mean of 40mm and 43mm for the ulipristal 5mg and 10mg groups, the mean change was -15mm and -18mm respectively, at the final follow-up visit.¹

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 UFS-QoL questionnaire (which was developed specifically for women with myoma) consists of 2 parts: 8 symptom severity questions and 29 health-related quality of life (HRQoL) questions. The symptom severity part of the questionnaire includes grading of bleeding, abdominal pressure, urination frequency and fatigue; the HRQoL part of the questionnaire evaluates the following domains: concern, activities, energy/mood, control, self-consciousness and sexual function. A level of 23 has been cited as normal for healthy women.² After four treatment courses, the mean change from baseline in the UFS-QoL symptom severity score was -29.81 in each treatment group.^{1,5} Improvement in the UFS QoLHRQoL total score followed a similar pattern.¹ 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, and these improvements were maintained throughout the study.¹

PEARL III included 209 pre-menopausal women aged 18 to 48 years, with at least one fibroid >3cm in diameter and none >10cm, HMB, and uterine size <16 weeks of gestation, who were eligible for fibroid surgery.⁴ The core PEARL III 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 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 and was reported in the published paper and its supplementary materials for all study patients as well as separately for norethisterone acetate and placebo groups. A total of 78% (164/209) patients achieved amenorrhoea at the end of the first treatment course; 132 patients entered the extension study and 107 were included in the intention to treat population for treatment course four, 90% of whom achieved amenorrhoea.⁴

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The pivotal PEARL IV study did not provide comparative safety data versus a relevant comparator.^{1,2}

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.¹

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.³ In addition, reversible increase of the endometrium thickness may occur during treatment and monitoring, including annual ultrasound, is recommended.³

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Most patients with uterine fibroids are asymptomatic, however in those patients with symptoms, the main ones include HMB, anaemia, abdominal pressure, abdominal pain, increased urinary frequency and infertility.⁶ The extension to the licensed indication makes ulipristal 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.¹ The submitting company has requested that SMC reviews 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 (defined as all currently available pharmacological treatments) and described as being normally focused on the control of HMB. Currently available drug treatments for symptomatic fibroids are all short-term and usually used pre-operatively. These include hormonal treatments: gonadotrophin releasing hormone (GnRH) agonists and progestogens; as well as tranexamic acid and non-steroidal anti-inflammatory drugs [NSAIDs]). Hysterectomy is the only treatment that removes fibroids permanently but it is unsuitable for patients who wish to preserve fertility and in those unfit for, or who do not wish to have, surgery. Other less invasive procedures are myomectomy and uterine artery embolisation (UAE). However, these may also be unsuitable options because of the potential for adverse events and risks to fertility.⁷

The pivotal PEARL IV study demonstrated that 73% of patients on the licensed dose of ulipristal achieved the secondary outcome of controlled bleeding after the fourth treatment course, and this was considered by the European Medicines Agency to be of clinical relevance.¹ The primary outcome of amenorrhoea at the end of all four individual treatment courses was achieved in approximately half of evaluable patients receiving the licensed dose of ulipristal. Previous short-term studies showed that ulipristal was superior to placebo in reducing menstrual bleeding and fibroid size (PEARL 1 study)⁸ and was non-inferior to monthly injections of leuporelin acetate for controlling uterine bleeding (PEARL II study).⁹ A placebo arm was considered unethical in the PEARL IV study.¹

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. However the lack of a clear comparator given the proposed positioning and the difficulties in comparing ulipristal with invasive treatments are acknowledged. There is little controlled published evidence regarding the interval before fibroid regrowth and symptom recurrence after the end of ulipristal treatment, although the submitting

company has advised that some data are now available indicating continuation of efficacy with longer treatment free intervals.¹⁰

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.

Clinical experts consulted by SMC considered that ulipristal is a therapeutic advancement as a treatment option to avoid surgery/invasive procedures which may involve hospital stays, post-operative illness, blood transfusion and other complications. This would be of benefit to the patient and the service.¹⁰

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.³ Annual ultrasound is recommended to monitor endometrial thickening.³

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing ulipristal with invasive procedures for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. 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 assumptions used for each subgroup were as follows:

- In the peri-menopausal group (assumed to account for 73% of patients), the comparators consisted of a weighted average of hysterectomy (80%), myomectomy (7%), and UAE (13%) and the analysis was conducted over a 3 year time horizon. The time horizon was based on the difference between the average age of patients receiving surgical intervention for fibroids (48 years) and the average age of menopause (51 years), although the impact of longer term complications of hysterectomy was also included.
- In the fertility group (18% of patients), the comparators were myomectomy (35%) and UAE (65%). A 1-year time horizon was selected for this analysis on the assumption that this group of patients would only receive treatment for up to 1 year before trying to conceive.
- In the comorbidity group (9% of patients), the comparator was no treatment and the time horizon was 8 years. The time horizon was based on the difference between the average age of patients in an observational study (43 years) and the average age of menopause (51 years).

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. A decision tree structure was used for the short term phase (1 year) covering the initial four courses of ulipristal treatment or the first year following the invasive procedures. A Markov model was used to

evaluate the treatments over the longer term. For the ulipristal arm of the model, the cycle length was the length of time required for each course of treatment (assumed to be 139 days). For the invasive procedures arm a 1 year cycle length was used.

In the ulipristal arm, after the first 4 courses of ulipristal treatment, patients were classified as treatment successes (where symptoms were resolved) or treatment failures (where symptoms were unresolved). 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 model for hysterectomy covered the year following the initial procedure and, as hysterectomy is curative, the model focused on complications following the procedure including a small risk of procedure-related death. For the UAE model, the model also included a proportion of patients experiencing technical failure of the procedure and then requiring an additional procedure. The risk of complications and side-effects following the procedure was also included. For the myomectomy model, patients were classified as being treatment successes or failures, and it also captured complications from the procedure. 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. The economic model used data from a secondary outcome which measured the percentage of patients in amenorrhoea at the end of each treatment course individually. This resulted in treatment success rates of 72%, 74%, 73%, and 70% for the first 4 treatment courses. For the comparator treatments, the majority of data were taken from a separate published open-label study comparing UAE and surgery. Hysterectomy was assumed to be curative, and for myomectomy and UAE the long-term treatment success rate was 92%. 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 (1.9% per annum) 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 (3.84% per annum).

The utility values used in the model were 0.956 for patients whose symptoms had resolved (amenorrhoea) and 0.874 for patients whose symptoms had not resolved. These estimates were based on EQ-5D data collected in the PEARL IV study. A utility decrement of 0.009 was also applied to patients who required an additional invasive procedure. This decrement was taken from the NICE guidance on UAE. Decrements associated with major and minor complications were also included.

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. No costs of treating adverse events associated with ulipristal were included as it was assumed patients would withdraw from treatment and require invasive procedures. Costs of invasive procedures and associated major and minor complications were included in the analysis. This included the costs of pelvic organ prolapse surgery and urinary incontinence surgery associated with hysterectomy. A gynaecology consultant appointment was included for patients initiating ulipristal treatment, with treatment continuation assumed to be carried out by a GP with 1 visit per cycle assumed. The cost of an ultrasound and follow-up annual consultant appointment was included in line with the Summary of Product Characteristics (SPC).

In the peri-menopausal group, the company estimated ulipristal would be cost-saving (-£534) but also associated with a QALY loss (-0.0136) compared to a weighted average of invasive

procedures. The resulting ICER is £39,411 (indicating ulipristal is cost-effective as the ratio is in the south-west quadrant of the cost-effectiveness plane where ulipristal is estimated to be less effective but also have a lower cost). The ICER in this analysis shows invasive procedures would not be considered cost-effective relative to ulipristal assuming a willingness to pay threshold of £30k.

In the fertility group, the company estimated ulipristal would be cost-saving (-£2,646) but also associated with a QALY loss (-0.0110) compared to a weighted average of invasive procedures. The resulting ICER is £240,608 (again indicating ulipristal is cost-effective as the ratio is in the south-west quadrant).

In the comorbidity group, the company estimated the cost per QALY of ulipristal compared to no treatment was £14,631 based on an incremental cost of £5,511 and a QALY gain of 0.3767.

The company provided sensitivity analysis which showed the results of the peri-menopausal group were sensitive to changes in a number of parameters. When the cost of hysterectomy was reduced by around 20%, using alternative utility values from the NICE model, or when the comparator was UAE alone, ulipristal was no longer cost-effective at a willingness to pay threshold of £30k. In the fertility group, ulipristal was not cost-effective when the time horizon was increased to 4 years. The results of the comorbidity group were also sensitive to the time horizon with the ICER increasing to £22k when a 1 year time horizon was 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 proportion of patients with symptom resolution based on the primary endpoint was lower (48.7% vs 70%) but the overall impact of using the secondary analysis was unclear. The company subsequently provided sensitivity analysis which reduced the response rate of each treatment course by 10%. This analysis showed the results remained relatively robust to the lower efficacy estimates.
- The time horizon may not be sufficient in the fertility group analysis. The time horizon was 1 year, but there may be a group of patients who are not planning to conceive within this time period and therefore may require treatment beyond 1 year. As noted above, when the time horizon for this analysis was increased to 4 years ulipristal was no longer cost-effective. However, the company noted that if patients required longer treatment, the interval between courses may increase, and therefore the 4 year time horizon analysis may overestimate the drug cost of ulipristal.
- The comparator of no treatment was not included in the analysis, which may not be appropriate as there may be a group of patients eligible for invasive procedures but who wish to avoid the risks associated with them. The company was asked to comment on this and their response indicated that the comorbidity analysis could be considered as a proxy analysis versus no treatment for all subgroups. However, the impact of including no treatment as a comparator within the weighted average treatment arm in the peri-menopausal and fertility subgroup analyses is unclear.

Despite these limitations, the economic case has been demonstrated.

Summary of patient and public involvement

A patient group submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) issued Clinical Guideline 44 in 2007 titled “Heavy menstrual bleeding: assessment and management”.⁷ The guidance states that should imaging show the presence of uterine fibroids then treatment should be based on the size, number and location of the fibroids. For women experiencing HMB, where no structural or histological abnormality is present or where fibroids are less than 3cm in diameter, the use of pharmaceutical treatments should be considered.

If pharmaceutical treatment (hormonal and non-hormonal) is deemed appropriate, treatments should be considered in the following order:

- levonorgestrel-releasing intrauterine system (LNG-IUS) providing long-term (at least 12 months) use is anticipated
- tranexamic acid or NSAIDs or combined oral contraceptives
- norethisterone (15mg) daily from days 5 to 26 of the menstrual cycle or injected long-acting progestogens.

Referral for non-medical treatment is recommended for women with large fibroids (>3cm) and/or menorrhagia causing distress despite symptomatic treatment and other significant symptoms including dysmenorrhoea or pressure symptoms; or for fibroid-associated fertility or obstetric problems. Myomectomy, hysterectomy and UAE should be considered if the bleeding is having a severe impact on a woman's quality of life. For interim treatment while awaiting referral, consider short-term medical treatment such as tranexamic acid or an NSAID.

If a woman expresses that hormonal treatments are not acceptable, then either tranexamic acid or NSAIDs can be used. Use of NSAIDs and/or tranexamic acid should be stopped if it does not improve symptoms within three menstrual cycles.

As changes to bleeding are common, particularly in the first few cycles of LNG-IUS use, women should be advised to persevere for at least six cycles to see the benefits of the treatment. When a first pharmaceutical treatment has proved ineffective, a second pharmaceutical treatment can be considered rather than immediate referral to surgery.⁷

The Faculty of Sexual and Reproductive Healthcare in its “UK Eligibility Criteria for Contraceptive Use” advise that uterine fibroids is a condition for which there is no restriction on the use of combined or progestogen-only hormonal contraceptives. There is no restriction on the use of the LNG-IUS providing there is no distortion of the uterine cavity. Where uterine fibroids distort the uterine cavity, the theoretical or proven risks are generally considered to outweigh the advantages. The provision of an LNG-IUS in this situation requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable.¹¹

The European Menopause and Andropause Society (EMAS) issued a position statement, “Management of uterine fibroids” in 2014.¹² It noted that the range of medical treatments allows flexible management of fibroid-related symptoms; the options include non-hormonal treatments: tranexamic acid or NSAIDs and hormonal treatments: contraceptive steroids, GnRH analogues, anti-progesterone, and selective progesterone receptor modulators. However, these medical options do not remove the tumours and symptoms may return when treatment is stopped. Surgical and radiologically guided procedures may be tailored to age, general health, and individual patient wishes. Hysterectomy is the most effective treatment, although in some cases myomectomy may be sufficient to control symptoms. Alternatives to surgery include UAE, myolysis and ablation by high-intensity focused ultrasound (guided with magnetic resonance imaging or ultra-sound). 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.¹²

Additional information: comparators

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

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Ulipristal acetate	Orally 5mg daily	342	1,370

Cost from evadis on 03.11.15. ‘Cost per course’ is based on four cycles of treatment.

Additional information: budget impact

The company estimated there would be 829 patients eligible for treatment in year 1, rising to 2,105 in year 5. The uptake rate was estimated to be 29% in year 1 (240 patients) and 60% (1,263 patients) in year 5.

The gross medicines budget impact was estimated to be £202k in year 1 and £1.06m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £157k in year 1 and £968k in year 5. The displaced medicine cost was the course of ulipristal or GnRH in the pre-operative setting.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. The European Medicines Agency (EMA) European Public Assessment Report. Ulipristal acetate (Esmya®). 23/04/2015, EMEA/H/C/002041/II/0028 www.ema.europa.eu
2. Donnez J, Hudecek R, Donnez O, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertility and Sterility 2015; 103(2):519-27 plus supplement
3. Ulipristal acetate 5mg tablets (Esmya®) Summary of product characteristics. Gedeon Richter (UK) Ltd. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 5 June 2015 plus original version 30 April 2013
4. Donnez J, Vazquez F, Tomaszewski J, et al. Long-term treatment of uterine fibroids with ulipristal acetate. Fertility and Sterility. 2014; 101(6):1565-73
5. **Commercial In Confidence*
6. BMJ Best Practice uterine fibroids <http://bestpractice.bmj.com/best-practice/monograph/567.html>
7. National Collaborating Centre for Women's and Children's Health. National Institute for Health and care Excellence (NICE) clinical guideline 44: Heavy menstrual bleeding: assessment and management. January 2007. www.nice.org.uk
8. Donnez J, Tatarchuk TF, Bouchard P, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. New England Journal of Medicine. 2012; 366(5):409-20.
9. Donnez J, Tomaszewski J, Vazquez F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. New England Journal of Medicine 2012; 366(5):421-32.
10. Trefoux Bourdet A, Luton D, Koskas M Clinical utility of ulipristal acetate for the treatment of uterine fibroids: current evidence. International Journal of Women's Health 26 March 2015
11. Faculty of Sexual and Reproductive Healthcare (FSRH). UK medical eligibility criteria for contraceptive use. 2009 <http://www.fsrh.org/pdfs/UKMEC2009.pdf>
12. Perez-Lopez FR, Ornat L, Ceausu I, et al. EMAS position statement: management of uterine fibroids. Maturitas. 2014; 79(1):106-16.

This assessment is based on data submitted by the applicant company up to and including 11 December, 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.