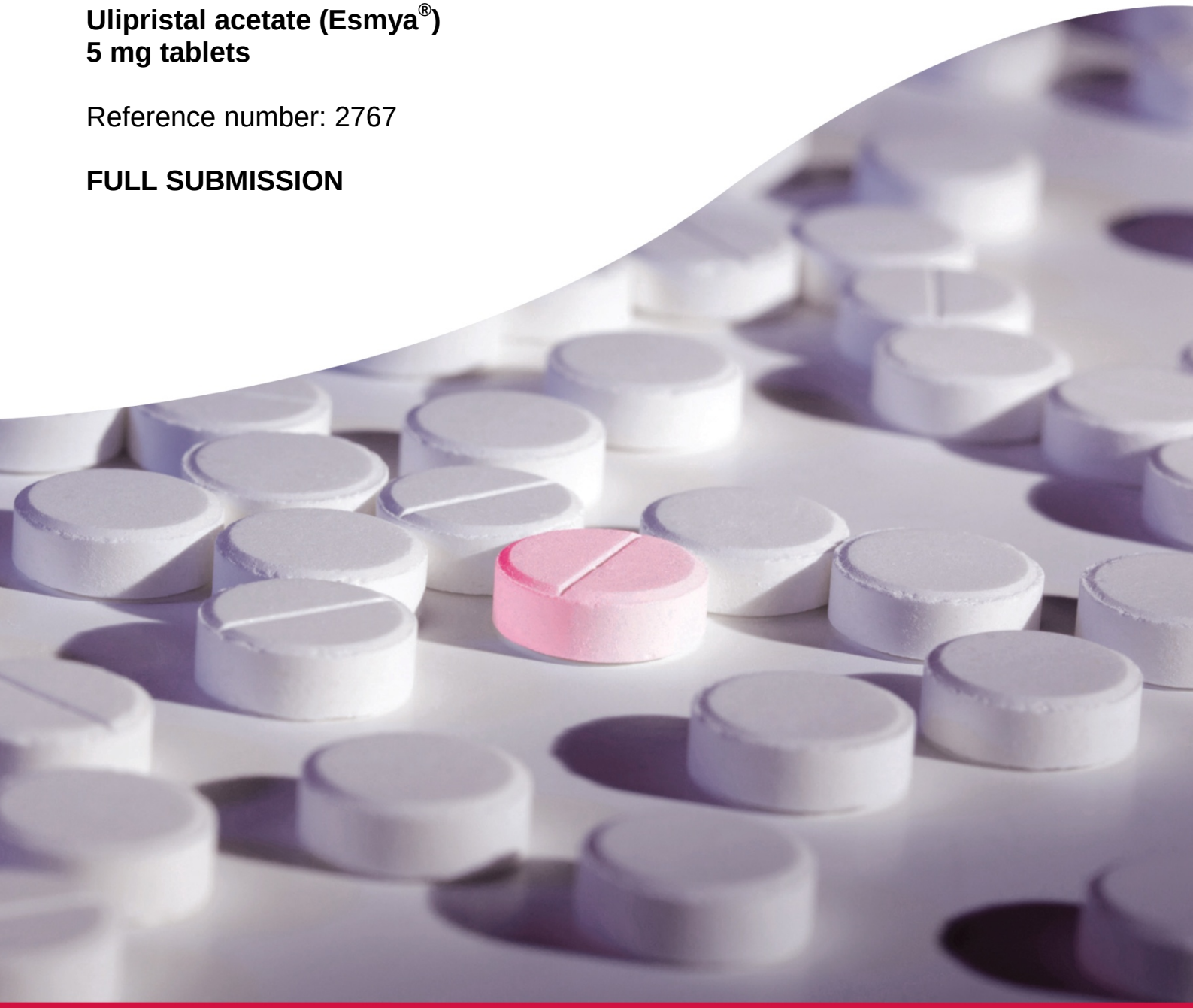
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ulipristal acetate (Esmya®) 5 mg tablets

Reference number: 2767

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Ulipristal acetate (Esmya®) 5 mg tablets

This assessment report is based on evidence submitted by Gedeon Richter UK Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ulipristal acetate (Esmya®) for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2].
Dosing	One 5 mg tablet to be taken orally once daily for treatment courses of up to three months each. Refer to the SPC for further information regarding treatment initiation and re-treatment courses[2].
Marketing authorisation date	27 May 2015[2].

2.0 DECISION CONTEXT

2.1 Background

Uterine fibroids are benign, monoclonal, hormone-sensitive, smooth muscle tumours of the uterus[1,3]. Uterine fibroids are often asymptomatic but symptomatic patients typically present with heavy uterine bleeding, anaemia, abdominal pressure, abdominal pain, increased urinary frequency, and infertility[1,3]. Heavy menstrual blood loss is one of the most frequently disabling symptoms of uterine fibroids[3]. Fibroids are the most common tumour of the female reproductive tract in pre-menopausal women and have been reported to affect 20% to 40% of women during their reproductive years[3]. In 2014/15 there were 1,311 consultant episodes attributed to uterine fibroids in NHS Wales[4].

The National Institute for Health and Care Excellence (NICE) clinical guidance 44 (CG44) for the assessment and management of heavy menstrual bleeding states that where no structural or histological abnormality is present, or for fibroids < 3 cm in diameter, a pharmaceutical treatment may be appropriate and the following options may be considered; levonorgestrel-releasing intrauterine system, provided long-term use is anticipated; tranexamic acid or non-steroidal anti-inflammatory drugs (NSAIDs) or combined oral contraceptives; and then norethisterone or injected long-acting progestogens[5]. The guidance states that gonadotrophin-releasing hormone analogue (GnRHa) can be considered prior to surgery or when all other treatment options for uterine fibroids, including surgery or uterine artery embolisation (UAE), are contraindicated. When pharmaceutical treatment is considered unsuitable or ineffective surgical intervention or UAE may be considered[5].

Current surgical interventions include endometrial ablation, myomectomy, and hysterectomy[3,5]. Endometrial ablation should be considered in women with heavy menstrual bleeding who have a normal uterus and small uterine fibroids (< 3 cm in diameter). For women with large fibroids (> 3 cm in diameter) and heavy menstrual bleeding, and other significant symptoms such as dysmenorrhoea or pressure

symptoms, referral for consideration of surgery or UAE as first-line treatment can be recommended[5].

Ulipristal acetate (Esmya®) is a selective progesterone receptor modulator that exerts a direct action on fibroids, reducing their size through inhibition of cell proliferation and induction of apoptosis[2]. Esmya® was originally licensed 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 one three-month course[3,6]. The license has been extended for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age[3,7]. The company has focused their submission on the use of Esmya® as a second-line treatment for those patients with moderate to severe symptoms who have failed on, or are unsuitable for first-line pharmaceutical treatments[1].

2.2 Comparators

The comparators included in the company submission to support the company's proposed place in therapy are surgical interventions including hysterectomy, myomectomy and UAE, and no treatment[1].

2.3 Guidance and related advice

- NICE. Clinical Guideline (CG) 44. Heavy menstrual bleeding: assessment and management (2007)[5]. A review of CG 44 is in progress; Expected April 2016[8].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of ulipristal acetate (Esmya®) for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of four phase III studies: PEARL I, II, III and IV[1]. PEARL I (placebo-controlled study) and II (active comparator controlled study) were presented in a previous submission, demonstrating the short-term efficacy and safety of Esmya® in the pre-operative setting[6]. PEARL III demonstrated the long-term efficacy and safety of ulipristal acetate 10 mg (unlicensed dose)[1]. The pivotal study, PEARL IV, provides information on the long-term efficacy and safety of Esmya® and ulipristal acetate 10 mg. PEARL I–III, and the 10 mg treatment arm in PEARL IV, are not discussed in relation to the clinical efficacy and safety of Esmya® as these studies do not support the licensed indication under consideration. In the absence of direct comparative data the applicant company conducted a literature review and identified two studies, HOPEFUL[9] and REST[10], which compared UAE to hysterectomy and UAE to surgical intervention, respectively. These studies enabled a naive indirect comparison and the HOPEFUL study was used to estimate comparative effectiveness within the economic model[1] (see section 4.0).

3.1 PEARL IV

This was a phase III, multicentre, randomised, double-blind study, investigating the efficacy and safety of repeated 12-week treatment courses of daily Esmya® and ulipristal acetate 10 mg for the long-term management of symptomatic uterine fibroids[1,3]. Patients were pre-menopausal and had at least one fibroid ≥ 3 cm in diameter and none > 12 cm with heavy menstrual bleeding and a uterine size < 16 weeks of gestation. The primary efficacy endpoint was the percentage of patients in amenorrhoea (defined as no more than one day of spotting within a 35-day period) at the end of two treatment courses and at the end of all four courses. Other key outcomes included the percentage of patients with controlled bleeding (defined as no episodes of heavy bleeding and a maximum of eight days of bleeding during the last 56

days of a course of treatment) at the end of two and four courses, and change from baseline in the size of fibroids and uterine volume, health-related quality of life (QoL), and pain[1,3].

Women between the ages of 18 and 50 years were randomly allocated in a 1:1 ratio to receive either Esmya® (n = 228) or ulipristal acetate 10 mg (n = 223) and matching placebos daily for up to four courses[1,3]. Each course lasted 12 weeks, and was separated by a treatment-free period until the start of the second menstruation following the end of the previous treatment course[1,3].

Results showed that 61.9% (122/197) of patients treated with Esmya® were in amenorrhoea at the end of two treatment courses, and 48.7% (95/195) were in amenorrhoea at the end of all four treatment courses[1,3]. At the end of two and four treatment courses 81.1% (150/185) and 67.1% (106/158) of patients, respectively, exhibited controlled bleeding. The median percent change in the total volume of the three largest fibroids was −38.0% at the end of treatment course one and −71.8% at the end of treatment course four[1]. The median percent change in uterine volume was −13.3% at the end of treatment course one and −25.1% at the end of treatment course four[1]. Improvement in patient reported health-related QoL and pain was demonstrated in the EuroQoL five dimensions questionnaire (EQ-5D), the Uterine Fibroid Symptom and QoL questionnaire (UFS-QoL), and the Short-form McGill Pain Questionnaire (SF-MPQ)[1,3]. Median EQ-5D visual analogue scale (VAS) scores improved from 80.0 at baseline to 90.0 and 92.0 at the end of course four and at the end of follow-up, respectively. Median symptom severity scores on the UFS-QoL decreased from 50.0 at baseline to 15.6 and 18.8 at the end of course four and at the end of follow-up, respectively. Median SF-MPQ scores reduced from 39.0 at baseline to 7.0 and 9.0 at the end of course four and at end of follow-up, respectively[1].

3.2 Comparative safety

The short-term safety of Esmya® (limited to one three-month course of treatment) has previously been demonstrated in PEARL I and II[1,3]. The PEARL III study provided supportive information on the longer-term safety of the higher dose of ulipristal acetate 10 mg. Only PEARL IV provided information on the long-term safety of repeated intermittent courses (maximum four) of Esmya®; the study demonstrated a similar safety profile to that observed for one treatment course of Esmya®[2].

In PEARL IV, Esmya® was well tolerated with nine (3.9%) patients discontinuing treatment and 12 (5.2%) withdrawing from the study due to on-treatment treatment-emergent adverse events (TEAEs)[1]. Tolerability of Esmya® was supported in off-treatment TEAE assessment, with only five patients discontinuing treatment or withdrawing from the study. The most commonly reported on-treatment TEAE that was considered related to Esmya® was hot flush, reported in 18 (7.8%) patients, followed by headache, reported in 13 (5.7%) patients. Reproductive system and breast disorders were the most commonly reported (n = 29; 12.6%) off-treatment TEAEs considered related to Esmya®[1]. The Committee for Human and Medicinal Products (CHMP) noted that PEARL IV did not reveal any unexpected safety findings and overall, the safety profile was reassuring[3].

The SPC states that Esmya® has a specific pharmacodynamic action on the endometrium and that a reversible increase of the endometrium thickness may occur under treatment[2]. The PEARL IV study did not reveal any unexpected safety concerns relating to endometrial safety and the median endometrium thickness (7–8 mm) was similar to screening levels at all time-points during the study and post-treatment follow-up. There were fewer subjects with endometrium thickness > 16 mm after successive treatment courses (4.9% and 3.5% of patients by the end of second and fourth treatment course, respectively)[3]. Data from the PEARL IV study did not report any increase in the occurrence of more serious conditions of the endometrium such as

hyperplasia with atypia or endometrial carcinoma[3]. As changes in endometrial thickness have been observed in previous short-term and long-term studies the SPC recommends periodic monitoring of the endometrium for repeated intermittent treatment. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period[2].

3.3 AWTTC critique

- The company has focused their submission on the use of Esmya® as a second-line treatment when patients are unsuitable for, or have failed to respond to, first-line treatment. The company has suggested that first-line treatment options are pharmaceutical medicines and that there are no pharmaceutical options for the management of this condition in the second-line setting[1]. Surgical intervention may be the only option for patients in the second-line setting and therefore surgical intervention was included as a comparator for evaluating cost-effectiveness[1].
- There are no efficacy or safety studies directly comparing Esmya® with surgical intervention in patients with moderate to severe symptoms.
- The PEARL IV study provides data to support the efficacy and safety of Esmya® for up to four intermittent treatment courses. In this study surgery was not planned for the majority of patients (90.9%) and only 7% of patients had previously received contraceptive medications in an attempt to control heavy menstrual bleeding within the year prior to study entry[1,3]. The patient population in PEARL IV may therefore not be representative of those patients expected to receive Esmya® in the second line setting i.e. as an alternative to surgical interventions.
- In line with the licensed indication, patients in the PEARL IV study had moderate to severe symptoms. In accordance with NICE CG44 a pharmaceutical treatment option would be used where no structural or histological abnormality is present, or for fibroids < 3 cm in diameter which are causing no distortion of the uterine cavity. Patients with more moderate to severe symptoms would usually be managed first-line by treatment with GnRHa and/or surgical intervention[5]. The company has not included GnRHa as a comparator; however their choice appears reasonable for the second-line setting in patients with moderate to severe symptoms.
- Clinical expert opinion, sought by AWTTC, suggests that comparator treatments for the licensed indication under consideration (intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age) are varied depending on the symptoms and the size and location of the fibroids; the list of comparators includes surgery in the form of hysterectomy or myomectomy, UAE, and symptomatic treatment with tranexamic acid, GnRHa or a Mirena® intrauterine delivery system.
- In PEARL IV repeated treatment was administered at the start of the second menstruation post completion of the previous treatment course (as per the study protocol). The company expect that, in clinical practice, repeated treatment will be initiated as required for the management of symptoms with off-treatment durations of at least two months recommended between courses and patients only restarting treatment on return of symptomatic disease[1].
- The applicant company also suggest that Esmya® will provide an attractive treatment alternative to the peri-menopausal group in NHS Wales; enabling patients to manage the debilitating 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[1].
- In the PEARL IV study the observed reduction in bleeding was associated with an improvement in haemoglobin levels in patients and correction of anaemia.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

The company submission describes a cost-utility analysis (CUA) of Esmya® compared to invasive treatments or no treatment for the second-line treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age in Wales. This represents a more restricted population than the indication, which is the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Consequently, the company submission is restricted to a second-line setting where patients are unsuitable for, or have failed to respond to, first-line treatment of moderate to severe symptoms of uterine fibroids.

The company submission includes three distinct patients groups: (i) a peri-menopausal group consisting of older women who do not want any more children and would therefore be offered surgical intervention, primarily with hysterectomy, and where Esmya® is compared to invasive procedures comprising hysterectomy, myomectomy and UAE; (ii) a fertility group consisting of younger women who wish to preserve their fertility and thus for whom hysterectomy is not an option, and where Esmya® is compared to invasive procedures comprising myomectomy and UAE; and (iii) a comorbidity group of women who cannot or do not wish to have invasive procedures, and where Esmya® is compared to no treatment.

The company developed a *de novo* cost effectiveness model to estimate the incremental costs and health outcomes over the time horizons of the model, which differed for the different patient groups: (i) three years for the peri-menopausal group; (ii) one year for the fertility group; and (iii) eight years for the comorbidity group. The different time horizons are based on the difference between the mean patient ages at the time they initiate treatment (48, 30 and 43 years, respectively) and the age of either menopause, at which point treatment is no longer required, or in the fertility group, at the time before attempting to conceive.

The economic model utilised a two stage approach to reflect both the initial treatment decisions that are made and the longer-term outcomes that those initial decisions lead to. The first stage of the model is a decision tree representing the clinical pathway in the short term, based on treatment success (symptom resolution) or failure (no symptom resolution), and complication rates for invasive procedures. For Esmya®, this covers the four courses of treatment, with each course comprising on-treatment for 84 days and 55 days off-treatment. For the invasive procedures comparator, this models the year immediately following the initial procedure. The second stage of the model utilises a Markov structure to evaluate clinical pathway in the longer term for Esmya® and the invasive procedures. The two health states included in the second stage of the model are “additional procedure” and “no additional procedure”. Patients who did not have symptom control at the end of the initial stage of the model were assumed to enter the “additional procedure” health state. Patients receiving four courses of Esmya® in the initial stage of the model (decision tree) are assumed to continue receiving it during the second stage of the model (Markov structure) whilst symptom control is maintained. Patients receiving hysterectomy in the initial stage of the model all had symptom resolution as hysterectomy is curative.

Efficacy data for Esmya® were obtained from the PEARL IV study, which included up to four courses of treatment with Esmya®. The primary endpoint in the study was the percentage of patients in amenorrhoea, which was used as a surrogate for successful treatment. In addition to patients undergoing invasive procedures in the study, all patients who withdrew from the study within the first four courses of treatment were also assumed to undergo invasive procedures. The Hirst model[9] was the primary source of efficacy and safety data for the invasive procedure comparators and was supplemented with data from another economic model when not available[11]. Patients

not receiving treatment with the comorbidity group are assumed to not experience symptom resolution as they have failed all non-surgical treatments.

Utility values were obtained from EQ-5D data collected in the PEARL IV study and based on whether patients were experiencing amenorrhoea at the time of the utility assessment. Other utility values, such as those associated with complications, were obtained from the published literature. Other data used to populate the model, such as long-term complication rates for hysterectomy, were obtained from published literature. Costs included in the model were those associated with treatment (medicine cost and cost of invasive procedure), monitoring, tests, investigations, procedural complications and subsequent invasive procedures. Unit costs used to populate the model were obtained from standard sources.

4.1.1 Results

Results of the base case analysis are presented in Table 1. The results suggest that treatment with Esmya® is cost-effective compared to invasive procedures for the peri-menopausal and fertility groups. However, as the incremental cost effectiveness ratios (ICERs) are in the south west quadrant, this means that Esmya® is less costly and less effective than invasive procedures*. In addition, the results suggest that Esmya® is cost-effective compared to no treatment for the comorbidity group, though in this instance it is more expensive and more effective than no treatment.

Table 1. Company-reported results of the base case analysis.

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	CE result at WTP £20k per QALY
Peri-menopausal group						
Esmya®	£4,047	2.6833				
Invasive procedures	£4,583	2.6963	−£536	−0.0130	£41,154 SW quadrant	Cost effective
Fertility group						
Esmya®	£1,411	0.9124				
Invasive procedures	£4,058	0.9230	−£2,646	−0.0106	£249,665 SW quadrant	Cost effective
Comorbidity group						
Esmya®	£5,511	6.4906				
No treatment	£0	6.1140	£5,511	0.3767	£14,631	Cost effective

CE: cost effective; ICER: incremental cost-effectiveness ratio; QALYs: quality adjusted life years; SW: south west; WTP: willingness to pay.

The company conducted scenario analyses to test key areas of structural uncertainty within the model. These included: (i) comparison to individual invasive procedures; (ii) use of utilities for symptom resolution from Hirst and colleagues[9]; (iii) use of data for rate of additional procedures from Hirst and colleagues[9] for all model arms; (iv) longer duration between treatment courses for Esmya®; (v) yearly ultrasound not required for Esmya®; and (vi) duration of treatment (time horizon) ranging from one to four years for each patient group. Esmya® remained cost-effective in all scenarios except for the use of utilities from Hirst and colleagues[9] for the peri-menopausal group, time duration of four years for the peri-menopausal and fertility groups, and time duration of one year for the comorbidity group. Results of these specific scenario analyses are presented in Table 2.

*Incremental cost-effectiveness ratios (ICERs) in the south west quadrant have opposite meanings to ICERs in the north east quadrant despite the same sign, and thus values above the ceiling ratio (i.e. > £20,000 per quality adjusted life year (QALY) are considered cost effective.

Table 2. Selected company-reported scenario analyses.

Parameter	ICER	CE results at WTP £20k per QALY	Plausibility
Peri-menopausal group			
Utilities for symptom resolution from Hirst et al[9]	£19,160 SW quadrant	Not cost effective	Plausible as utilities based on treatment success with surgery which is more appropriate for invasive procedures comparator.
Four year duration of treatment	Dominated	Not cost effective	Plausible as difference between patient age at time treatment initiated and the age of menopause is variable.
Fertility group			
Four year duration of treatment	Dominated	Not cost effective	Plausible as difference between patient age at time treatment initiated and the time before attempting to conceive is variable.
Comorbidity group			
One year duration of treatment	£22,371	Not cost effective	Plausible as difference between age at time treatment initiated and the age of menopause is variable.
CE: cost effective; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; SW: south west; WTP: willingness to pay.			

The company conducted one way sensitivity analysis and measured the impact of varying model parameters, to both their lower and upper bound, on the net monetary benefit (NMB) at a willingness to pay (WTP) threshold of £20,000 per QALY. The results within the peri-menopausal group were most sensitive to the hysterectomy procedure cost and the cost of additional procedures. In the vast majority of cases, Esmya® remained the most cost-effective option within the lower and upper bounds of the parameters tested. The results within the fertility group were most sensitive to UAE and myomectomy procedure costs and wait time before invasive procedures. Esmya® remained the most cost-effective option within the upper and lower bounds of the parameters tested. The results within the comorbidity group were most sensitive to the utility values for patients who are and are not successfully treated. Esmya® remained the most cost-effective option within the upper and lower bounds of the parameters tested.

Probabilistic sensitivity analysis undertaken for the base-case analysis indicates that at a WTP threshold of £20,000 per QALY, Esmya® had a 73% chance of being the most cost effective treatment for the peri-menopausal group. For the fertility and comorbidity groups, the chance that Esmya® will be the most cost effective treatment is 100% and 95%, respectively.

4.1.2 AWTTC critique

The reliability of the company's estimate of the cost-effectiveness of Esmya® compared to invasive procedures and no treatment is dependent on the assumptions around comparability of data used in the economic model.

Limitations of the economic evidence include:

- There is a lack of comparative data for Esmya® and invasive procedures for the second-line treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- The company limits invasive procedures included in the comparator arms to hysterectomy, myomectomy and UAE and does not consider including hysterscopic resection of fibroids or endometrial ablation.
- The economic analysis is limited to a restricted population of the licensed indication. Consequently, the results of the analysis do not apply to the full licensed indication.
- The data from the PEARL IV study used to populate the economic model may not be fully representative of those patients eligible for second-line treatment (see section 3.3).
- In the model, clinical effectiveness is based on successful treatment (or symptom resolution). However, this is based on amenorrhoea for Esmya® and no further invasive procedures for the invasive procedures comparator. Consequently, they are not directly comparable and no indirect comparison was undertaken.
- The duration of treatment (time horizon) for the different patient groups is based on estimates of the average age of patients at the time of initiation of treatment. However, there is no direct evidence to support this for each of the patient groups and this is likely to be highly variable. In particular, the duration of treatment (time horizon) for the fertility group of one year does not take account of the fact that fibroids can continue to be present post-pregnancy. As women in the fertility group were many years from menopause, this considerably underestimates the duration of treatment (time horizon). The analysis utilises different cycle lengths for Esmya® and the comparators. However, the overall duration of treatment is the same for Esmya® and comparators for each patient group.
- The analysis assumes that all patients who fail to respond or experience fibroid regrowth, with Esmya® or invasive procedures, go on to receive alternative invasive procedures. In reality, this may not be the case or may not occur within the time horizon of the analysis.
- Utility values used in the economic model are associated with amenorrhoea or no amenorrhoea. Consequently, they don't accurately reflect the utility values for successful treatment for the invasive procedures, which in the model is based on whether or not an additional procedure was required due to lack of symptom resolution. Furthermore, the utility decrements associated with complications were obtained from the Hirst et al[9] model but applied to utility values from the PEARL IV study, and thus may not be a valid representation of utility scores.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of ulipristal acetate for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company reported the total number of consultant episodes in Wales in 2014/15 with a primary diagnosis of uterine fibroids to be 1,311[1]. Prior market research conducted by the company suggested that approximately 56% of patients with uterine fibroids had moderate to severe symptoms. This results in an estimated 734 women

eligible for treatment. The company identified three patients groups as being the most likely placement for Esmya® and estimated their respective share of the eligible population: peri-menopausal group as 40% of the eligible population; fertility group as 10% of the eligible population, and comorbidity group as 5% of the eligible population. This results in 404 women potentially eligible for treatment with Esmya®. The company estimates that uptake will range from [commercial in confidence figure removed] in year one to [commercial in confidence figure removed] in year five. Thus the number of patients treated with Esmya® is estimated to range from 117 in year one to 519 in year five. This includes patients still on treatment from previous years.

The company has based its budget impact analyses on the assumptions as used in the cost-effectiveness model. Consequently, the duration of treatment with Esmya® is four years for the peri-menopausal group, one year for the fertility group and eight years for the comorbidity group.

5.1.2 Results

The company estimates the acquisition costs of treatment (and monitoring) with Esmya® to be £1,369 per patient in year one. This compares to £4,165 for hysterectomy, £4,056 for myomectomy, £3,736 for UAE and £0 for no treatment. The estimated number of patients and the associated costs as described by the company in their budget impact analysis are summarised in Table 3.

Table 3. Company-reported net costs associated with the use of Esmya® for second-line treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	734	734	734	734	734
Number of patients within 3 identified patient groups	404	404	404	404	404
Uptake	¶¶	¶¶	¶¶	¶¶	¶¶
Treated patients (includes patients still on treatment from previous years)	¶¶	¶¶	¶¶	¶¶	¶¶
Net costs					
Medicine costs	£111,136	£210,239	£303,141	£359,702	£406,991
Surgery costs	−£974,372	−£784,380	−£593,778	−£496,165	−£401,681
Administration and monitoring costs	£17,335	£73,012	£110,063	£129,481	£146,445
Overall net cost	**−£845,901**	**−£501,128**	**−£180,574**	**−£6,982**	**£151,755**
¶¶. Commercial in confidence figure removed.					

The company conducted scenario analyses to assess the impact of varying input parameters on the overall budget impact. The scenarios considered were the two key areas of uncertainty identified within the cost-effectiveness analysis, namely: (i) the duration of treatment with Esmya®; and (ii) the spacing of treatment with Esmya® over time. In all scenarios, the cumulative net budget impact over the first four years remains negative with a net cost in year five. The main driver of the projected cost savings were the high costs associated with the invasive procedures.

5.1.3 AWTTC critique

- The company has made reasonable effort to estimate the number of eligible patient numbers by basing this on Welsh data on the number of hospital episodes with a primary diagnosis of uterine fibroids.
- The estimate of the number of eligible patients is based on patients with moderate to severe fibroids so does not reflect those successfully treated with first-line treatments. Hence, this may be an overestimate. The validity of the

anticipated savings is dependent on assumptions about treatment duration for each of the patient groups.
- The cost estimates are derived from the company's cost-effectiveness analysis, therefore the limitations and uncertainties associated with the cost-effectiveness analysis also apply to the budget impact analysis.

5.2 Comparative unit costs

Table 4 includes example acquisition costs of other pharmacological products for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. However, these products are used as first-line treatments and thus aren't comparators for this submission. The example acquisition costs are based on a three month treatment period. The equivalent cost per patient for a patient receiving Esmya® for three months would be £342.39.

Table 4. Examples of acquisition costs per patient of pharmacological products for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Regimens	Example dose	Cost per patient per three month course
Ulipristal acetate (Esmya®) Oral tablets, 5 mg	Once daily for up to three months	£342.39
Leuprorelin acetate (Prostrap® SR DCS) Pre-filled syringe, 3.75 mg	3.75 mg as single injection every month for three to four months	£225.72
Triptorelin acetate (Decapeptyl® SR) Vial, 3 mg	3 mg injection every 28 days for minimum of three months.	£207.00
Goserelin acetate (Zoladex®) Biodegradable depot, 3.6 mg	3.6 mg injection every 28 days for maximum of six months	£195.00
Costs based on British National Formulary list prices, November 2015[12]. Costs of administration and monitoring are not included. This table does not imply therapeutic equivalence of drugs at the stated doses. See relevant SPCs for full dosing details[2,13–15].		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, ulipristal acetate (Esmya®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

The company do not anticipate that ulipristal acetate (Esmya®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there is one study from which additional evidence is likely to be available within the next 6–12 months. A second extension to the PEARL III study is currently ongoing. Although this study will not provide additional evidence for Esmya® it will provide additional long-term safety data for ulipristal acetate[16].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 26 October 2015
Date range of evidence search: No date limits were applied to database searches.

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Appendix: Previous AWMSG secretariat assessment report (published June 2013)

This report was published as part of a previous AWMSG appraisal of ulipristal acetate (Esmya®) (Advice number 1913). The advice from this appraisal has been superseded by advice number 0716. The original appraisal documentation is included here for completeness.

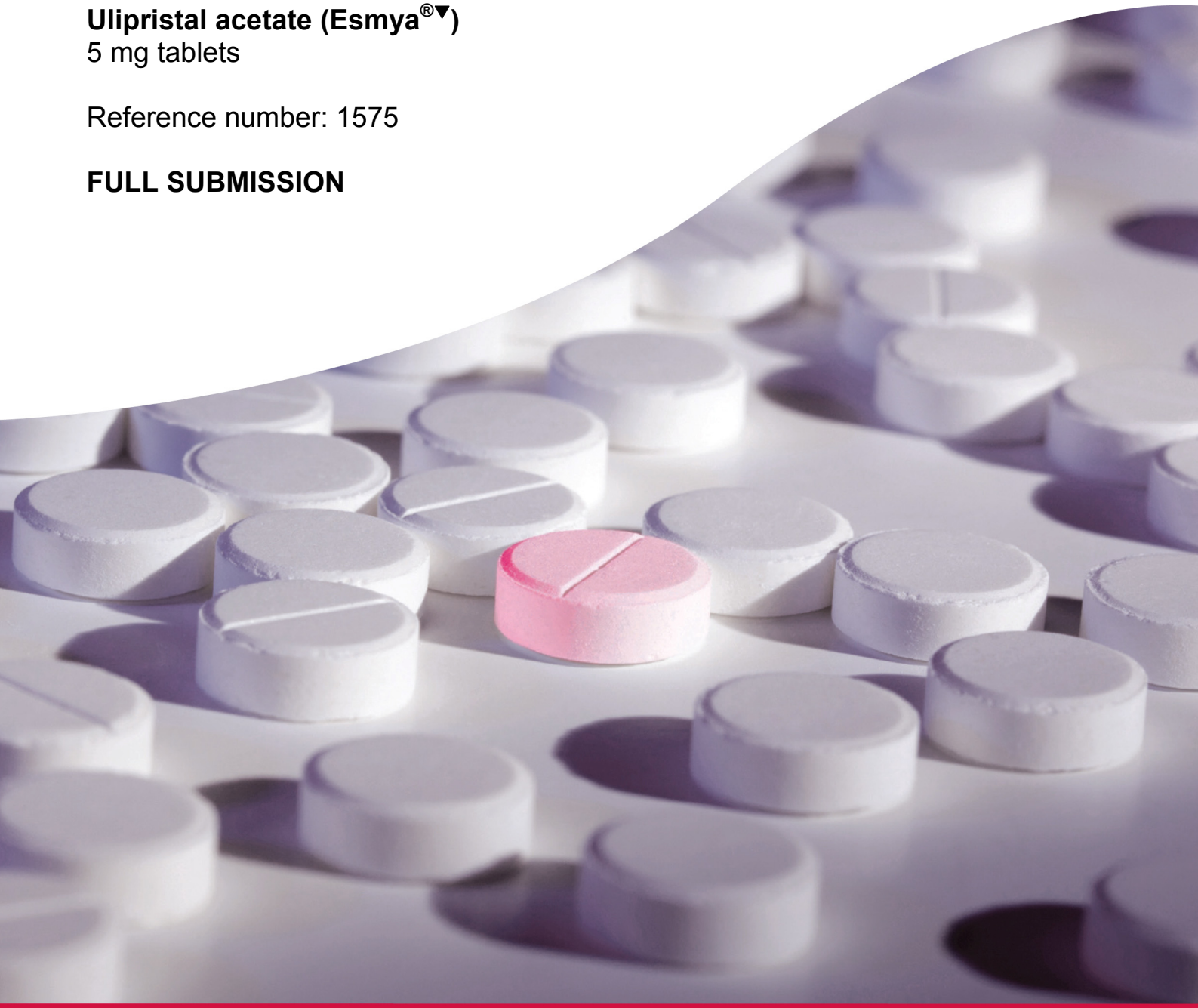
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ulipristal acetate (Esmya®▼)
5 mg tablets

Reference number: 1575

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Ulipristal acetate (Esmya®▼) 5 mg tablets

This assessment report is based on evidence submitted by Gedeon Richter (UK) Ltd on 15 January 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ulipristal acetate (Esmya®▼) is indicated for 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[2].
Dosing	The treatment consists of one 5 mg tablet to be taken orally once daily for up to three months. Treatment should be started during the first week of a menstrual cycle[2].
Marketing authorisation date	23 February 2012[2].

2.0 DECISION CONTEXT

2.1 Background

Uterine fibroids (uterine leiomyoma) are benign, hormone-sensitive smooth muscle tumours of the uterus[3,4]. When symptomatic, the primary symptoms of fibroids include heavy menstrual bleeding, anaemia, abdominal pain, increased urinary frequency and infertility. Fibroids are the most common tumour of the female reproductive tract in premenopausal women and are reported to affect 20%–40% of women during their reproductive years, although estimates vary[3,4]. During 2010–2011, there were 1,400 hospital admissions with a primary diagnosis of uterine leiomyoma in Wales[5].

The National Institute for Health and Care Excellence (NICE) state that if uterine fibroids are present, appropriate treatment should be planned based on the number, size and location of the fibroids[6]. Current surgical treatment options for symptomatic fibroids include hysterectomy, myomectomy and uterine artery embolisation[4,6]. NICE also recommends that pretreatment with a gonadotrophin-releasing hormone analogue (GnRHa) for three to four months before hysterectomy and myomectomy should be considered where uterine fibroids are causing an enlarged or distorted uterus. These pretreatments reduce the size of fibroids, make surgery easier and allow for use of a less invasive vaginal procedure[6].

Ulipristal acetate is a selective progesterone receptor modulator (SPRM) that interacts with the progesterone receptors in the fibroid cells, triggering apoptosis and inhibiting proliferation[2,4]. SPRMs have a direct effect on the endometrium; they reduce gonadotrophin secretion and inhibit ovulation while maintaining serum oestrogen levels at moderate concentration corresponding to mid follicular phase levels[4].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Goserelin acetate (Zoladex®).
- Leuprorelin acetate (Prostap® SR DCS).

2.3 Guidance and related advice

- NICE. Clinical Guideline 44. Heavy menstrual bleeding (2007)[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

As evidence of comparative effectiveness, the company submission presents two phase III studies: PEARL I, which evaluated ulipristal acetate against placebo, and PEARL II, which compared ulipristal acetate and leuprorelin acetate for the treatment of symptomatic uterine fibroids before surgery[1,7,8]. PEARL I will not be discussed further, as it does not inform the comparison of ulipristal acetate with an active comparator.

3.1 PEARL II

PEARL II was a randomised, parallel-group, double-blind, double-dummy, active-comparator-controlled phase III trial, which was designed to assess the efficacy and safety of ulipristal acetate in premenopausal women (aged 18–50 years) with symptomatic uterine fibroids before surgery[7]. Patients were randomised 1:1:1 to receive one of three treatment groups: a once-monthly intramuscular injection of leuprorelin acetate 3.75 mg plus once-daily oral placebo (n = 101) or ulipristal acetate as a once-daily oral dose of 5 mg or 10 mg plus a once-monthly intramuscular saline injection (5 mg: n = 98; 10 mg: n = 104). Treatment was initiated within four days of the start of the patient's menstrual period and was continued until week 13, after which patients could have surgery[7]. The licensed dose of ulipristal acetate is 5 mg, and therefore results from the 5 mg treatment group are most relevant; the 10 mg treatment group is not discussed further.

The primary efficacy endpoint was the proportion of patients with control of uterine bleeding at week 13, which was defined as a pictorial blood-loss assessment chart score (PBAC; monthly scores range from 0 to > 500, with higher numbers indicating more bleeding[8]) (summed over the preceding 28-day period) of < 75. In the per-protocol population, the proportion of patients with controlled bleeding at week 13 was 84/93 (90%) in the ulipristal acetate 5 mg arm and 82/92 (89%) in the leuprorelin acetate arm, with a treatment difference of 1.2% (95% CI: −9.3%–11.8%), which fulfilled the prespecified criterion for demonstration of noninferiority of ulipristal acetate to leuprorelin acetate (the lower limit of the 95% CI greater than −20%). This was supported by analysis of the modified intent-to-treat population. Leuprorelin acetate-treated patients demonstrated a larger reduction in fibroid and uterine volume in comparison to ulipristal acetate (see Table 1)[7]. However, amenorrhoea was induced more rapidly in patients in the ulipristal acetate arm than the leuprorelin arm (median time 7 and 21 days in each group, respectively), and excessive bleeding was controlled significantly more rapidly ($p < 0.001$). Additionally, median PBAC scores at week 13 were 0 for both treatment groups[1,7]. Both treatments were similarly effective at reducing pain associated with fibroids and normalising quality of life[7]. Refer to Table 1.

Table 1. Primary and secondary efficacy endpoints in the per protocol population.

	Ulipristal acetate (n = 93)	Leuprorelin acetate (n = 93)	Treatment difference (95% CI)
Primary endpoint			
Patients with control of uterine bleeding at week 13	84 (90.3%)	82 (89.1%)	1.2% (−9.3%–11.8%)
Secondary endpoints			
Median change from baseline in bleeding pattern (PBAC score)	−268	−274	6 (−54–63)
Proportion of patients with amenorrhea defined as PBAC score ≤ 2	75%	80%	−5.2 (−18.7–8.6)
Median change from baseline in myoma volume	−36%	−53%	NR
Median change from baseline in uterine volume	−20%	−47%	NR
Median change from baseline in global pain score	−5.0	−5.5	0.2 (−2.0–3.0)
Change from baseline in quality of life	23.7 ± 26.9	23.2 ± 28.2	2.5 (−7.3–12.3)
PBAC: pictorial blood-loss assessment chart; NR: not reported			

3.2 Comparative safety

The safety of ulipristal acetate 5 mg versus leuprorelin acetate 3.75 mg was assessed during the PEARL II study[1,4,7]. In the intention-to-treat population, adverse events (AEs) were observed in 76/97 (78.4%) of patients in the 5 mg ulipristal acetate arm and 90/101 (89.1%) of patients in the leuprorelin acetate arm. Two co-primary safety endpoints were investigated; oestradiol levels at the end of treatment and the percentage of patients experiencing moderate to severe hot flushes during the treatment period. At week 13, median oestradiol values were 64.0 picograms/ml in patients receiving ulipristal acetate; this decreased to postmenopausal levels (25.0 picograms/ml) in patients receiving leuprorelin acetate ($p < 0.001$). Additionally, significantly fewer ulipristal acetate-treated patients reported hot flushes versus the leuprorelin acetate arm (moderate to severe: 11% versus 40% [$p < 0.001$]; total incidence: 26% versus 65%)[1,4,7].

Fewer patients receiving ulipristal acetate discontinued treatment due to AEs (one patient versus six patients in the leuprorelin acetate arm); however, this difference was not found to be statistically significant[7]. After hot flushes, the most frequently reported AEs were headache (26% in the ulipristal acetate arm versus 29% in the leuprorelin acetate arm), abdominal pain (6% versus 14%) and nausea (6% for both treatment groups). The median level of the bone resorption marker, type 1 collagen C-telopeptide (CTX) was found to be significantly higher in patients receiving leuprorelin acetate than for those patients receiving ulipristal acetate[7]; however, analysis of other bone resorption markers found no effect on bone turnover with either group[4]. Mean endometrial thickness at week 13 was elevated in the ulipristal acetate group in comparison to the leuprorelin acetate group (9.4 mm versus 5.1 mm; $p \leq 0.001$)[7]. Further, endometrial thickness > 16 mm was reported in 11.3% of patients receiving ulipristal acetate, versus one case (< 1%) of leuprorelin acetate-treated patients; however, this effect was reversible once treatment had stopped and menstrual periods resumed[2,4].

In the placebo-controlled PEARL I study, the frequency of AEs was found to be comparable between treatment groups (49.5% in the ulipristal acetate arm versus 45.8% for placebo)[8].

3.3 AWTTC critique

- In their submission, the applicant company have provided comparative data between ulipristal acetate and leuprorelin acetate[1]. No comparative clinical effectiveness data have been provided between ulipristal acetate and other GnRHa therapies. However, the company note that, in the British Medical Journal Clinical Evidence publication, the GnRHas are considered as a class, and therefore, the superiority of one GnRHa to another has not been highlighted; all GnHRas are presumed to have a comparable therapeutic effect[9].
- Ulipristal acetate was found to be noninferior in comparison to leuprorelin acetate in terms of control of uterine bleeding, but demonstrated a more rapid effect on controlling excessive bleeding and inducing amenorrhoea. Leuprorelin acetate-treated patients demonstrated a significantly larger reduction in uterine volume than the ulipristal acetate group. Although leuprorelin acetate-treated patients also demonstrated numerically larger reductions in fibroid size, this was not statistically significant[7].
- Significantly fewer ulipristal acetate-treated patients reported hot flushes compared to leuprorelin acetate-treated patients. Ulipristal acetate did not exhibit the same increased levels of the bone resorption marker CTX observed in leuprorelin acetate-treated patients. No effect on other bone resorption markers was observed in either group[7].
- The effects of ulipristal acetate, for example reduction of bleeding, were found to be sustained for up to one month after discontinuation[4]. Additionally, in the subgroup of patients who did not subsequently undergo surgery, reduction in fibroid size was better maintained in patients who had received ulipristal acetate compared to leuprorelin acetate[1,4]. In the majority of ulipristal-acetate treated patients, reduction in fibroid volume was maintained for six months after the end of treatment[7].
- The Committee for Medicinal Products for Human Use (CHMP) concluded that differences in the pharmacological effect of ulipristal acetate and leuprorelin acetate, regarding reduction of the myoma and uterine volume, may be of importance for choice of preoperative treatment and that a positive effect on surgical performance has still to be proven, as the studies submitted at time of licensing were not powered to demonstrate this effect[4].
- There was no long-term follow-up of patients treated with ulipristal acetate in the clinical studies and so information on efficacy and safety is limited to 13 weeks[1,7]. Therefore, the Summary of Product Characteristics (SPC) states that, due to a lack of long-term safety data, the duration of treatment with ulipristal acetate should not be longer than three months[2]. It should be noted that leuprorelin acetate is usually administered for three to four months, but may be administered for up to a maximum of six months[10].
- Ulipristal acetate is an oral tablet taken once daily; this may be more preferable for patients than treatment with a GnRHa, such as leuprorelin acetate, which requires administration by subcutaneous or intramuscular injection on a once-monthly basis. The company reports GnRHa therapies are mostly administered by a healthcare professional[1,2].
- The SPC for ulipristal acetate states that this treatment is not recommended in patients with severe renal impairment or moderate to severe hepatic impairment unless closely monitored[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost minimisation analysis (CMA) of ulipristal acetate 5 mg daily for three months compared against the GnRHa therapies leuprorelin acetate (3.75 mg SR depot injection), triptorelin acetate (Decapeptyl®; 3 mg SR injection) and goserelin acetate (3.6 mg implant) given monthly for three to four months for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age[1]. These comparators were chosen by the company based on IMS 2010 and 2011 Welsh prescribing data, and a questionnaire survey of Welsh consultant gynaecologists. The GnRHa with the lowest list price, goserelin acetate, is used as the comparator in the base case analysis, with the costs of the other comparators tested in sensitivity analyses.

The CMA approach assumes equal efficacy between ulipristal acetate and other GnRHa therapies based on demonstration of the noninferiority of ulipristal acetate 5 mg compared with leuprorelin acetate in reducing fibroid-associated bleeding in the phase III trial, PEARL II[7]. There are no comparative data for ulipristal acetate and goserelin acetate or triptorelin acetate; the GnRHas are all assumed to be therapeutically equivalent based on published reviews[11]. Dosing, frequency and average treatment length were based on the relevant product SPCs, supplemented by the Welsh clinicians' survey. The time horizon of the analysis is assumed to be 3.82 months in the base case analysis based on expert opinion of treatment length with GnRHas. All treatments are assumed to have a similar overall safety profile.

Drug prices, including add-back hormone replacement therapy (for 46% of patients, based on expert opinion) to counter menopausal symptoms and the risk of loss of bone mineral density that may occur with GnRHas, are taken from the British National Formulary (BNF) 64[12]. Resource use estimates are primarily based on expert opinion sought through the Welsh consultant gynaecologists' survey. A third of GPs are assumed to charge a Directed Enhanced Services (DES) fee for administering GnRHas. Unit costs are taken primarily from the English National Schedule of Reference Costs[13] and Unit costs of Health and Social Care[14].

4.1.2 Results

The results of the base case analysis are presented in Table 2. The results 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.

Table 2. Base case analysis results.

Base case comparison	Total costs per treatment course			Plausibility
	Ulipristal acetate	Goserelin acetate	Difference	
Treatment (drug) costs	£342.39	£248.30	+£94.04	Assumption of equivalence of efficacy of all GnRHa treatments with ulipristal acetate is based on a randomised controlled trial versus leuprorelin acetate, which has been extrapolated to the comparison against goserelin acetate used in the base case.
Secondary care costs	£247.00	£314.84	−£67.84	
Primary care costs	£30.00	£115.74	−£85.74	
Total cost	**£619.39**	**£678.88**	**−£59.49**	

The company reported the results of the comparisons with the other two comparators: leuprorelin acetate and triptorelin acetate in a sensitivity analysis (see Table 3). A range of one way sensitivity analyses and scenario analyses are also reported. In most of these analyses, ulipristal acetate remains cost saving. Results of the key sensitivity and scenario analyses are presented in Table 3.

Table 3. Sensitivity and scenario analyses results.

	Total costs per treatment course			Plausibility
	Ulipristal acetate	Comparator	Difference	
Sensitivity analysis				
Length of treatment course (goserelin acetate) 3 months 4 months	£619.39 £619.39*	£602.04 £695.76	**+£17.35** **−£76.37**	The shorter treatment duration (three months) may be a plausible assumption based on the SPCs of the comparator treatments.
Price of GnRHa Leuprorelin acetate (£75.24) Triptorelin acetate (£69.00)	£619.39 £619.39	£718.01 £694.17	**−£98.62** **−£74.78**	Assumption of equivalence of efficacy of all GnRHa treatments with ulipristal acetate is based on a randomised controlled trial versus leuprorelin acetate. This has been extrapolated to the other comparator, triptorelin acetate.
First injection in hospital = 100% 0% require an additional appointment 100% require an additional appointment	£619.39 £619.39	£612.49 £692.49	**+£6.90** **−£73.10**	Base case assumption of receiving the first injection in a subsequent hospital visit is plausible; however, the percentage of patients requiring this additional appointment is uncertain.
First injection at GP practice 100% 50%	£619.39 £619.39	£636.44 £657.67	**−£17.05** **−£38.28**	No data exist on the percentage of patients receiving first injection at GP practice. Base case estimate is 0%. Ulipristal acetate remained cost saving over the range reported.
Use of add-back 30% of women 60% of women	£619.39 £619.39	£672.56 £684.43	**−£53.17** **−£65.04**	No data exist on the percentage of patients receiving add-back therapy. Base case estimate is 46%. Ulipristal acetate remained cost saving over the range reported.
GP charge DES fee 0% of practices 20% of practices 50% of practices	£619.39 £619.39 £619.39	£651.67 £668.17 £692.91	**−£32.28** **−£48.78** **−£73.52**	No reliable data exist on the percentage of practices charging DES fees. Base case estimate is 33%.
Scenario analysis				
Lowest comparator cost scenario *Assumptions:* -The first injection is given at hospital - All women have this injection at the first appointment with no additional cost. - Subsequent injections are given at a GP surgery and none are charged under DES.	£619.39	£585.27	**+£34.12**	Base case assumption of receiving the first injection in a subsequent hospital visit is plausible. Same limitation as base case where assumption of equivalence of efficacy of all GnRHa treatments with ulipristal acetate is based on a randomised controlled trial versus leuprorelin acetate.
* The duration of treatment with ulipristal acetate should not be longer than three months				

4.1.3 AWTTC critique

The reliability of the company's CMA is dependent on the extent to which ulipristal acetate is considered to be therapeutically equivalent, in terms of effectiveness and safety, to the comparator GnRHa treatments. Direct comparative data are available for ulipristal acetate and leuprorelin acetate only, and there are no direct comparative data for the other GnRHas. Resource use estimates are based on expert opinion, which may introduce a degree of uncertainty; however, ulipristal acetate remained cost saving compared with the comparators in most sensitivity analyses.

Strengths of the economic evidence include:

- The availability of direct comparative evidence from a phase III trial that compared ulipristal acetate against a GnRHa treatment, leuprorelin acetate.
- The base case analysis conservatively uses the least costly GnRHa comparator.
- A range of sensitivity and scenario analyses has been conducted to explore the impact of changing key assumptions and parameter values.

Limitations of the economic evidence include:

- There is a lack of comparative data for ulipristal acetate and goserelin acetate and triptorelin acetate, and also between the different GnRHas. The company based its analysis on the assumption of equivalent efficacy of ulipristal acetate and all three GnRHa treatments that are considered.
- All resource use estimates, e.g. treatment duration and proportion of women prescribed each GnRHa, are based on the expert opinion of 15 Welsh gynaecologists, in the reported absence of alternative sources.
- The length of treatment in the base case is considered to be 3.82 months; however, shorter treatment durations are plausible based on the SPCs of comparator treatments. For example, goserelin acetate is licensed for use for three months. Reducing treatment duration to three months has been explored by the company in sensitivity analysis, which revealed that this would result in an additional cost of £17 for use of ulipristal acetate compared to goserelin acetate.
- The CMA approach does not take account of any differences in patient preference for the different administration regimens.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have identified a conference abstract reporting the results of a cost utility analysis of ulipristal acetate 5 mg within its current licensed indication[15]. The study was conducted in Hungary and used a Markov state-transition economic model to assess the cost-effectiveness of using ulipristal acetate 5 mg compared to pre-surgical observation and immediate hysterectomy over a ten-year time horizon using a discount rate of 3.5%. The results showed that ulipristal acetate 5 mg was predicted to achieve an additional 0.021 quality-adjusted life-years (QALYs) resulting in an incremental cost-effectiveness ratio (ICER) of €19,208/QALY and €4,087/QALY compared with pre-surgical observation and hysterectomy, respectively. No comparison is reported versus other pharmacological treatments (e.g. GnRHa treatments). Given the difference in the structure of the health services in Hungary and Wales and the different comparators considered, the results are not applicable to the Welsh context.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates that around 784 women in Wales are eligible for treatment with ulipristal acetate[1]. This is based on a total number of hospital episodes with a primary diagnosis of uterine fibroids recorded in Wales in 2010/2011 of 1,400 and a prevalence of 56% for moderate/severe symptoms in patients with uterine fibroids, based on the company's own market research undertaken in 2008[5]. The company assumed that the annual number of eligible cases is constant in the five years 2013–2017 inclusive.

Based on the company's survey of Welsh gynaecology consultants, an average of 43% of women with moderate/severe symptoms of uterine fibroids scheduled for surgery would receive a pre-operative course of GnRHa, equivalent to 337 patients. The company expects its market share to increase from 9% in the first year (2013) to 43% in year five (2017); hence, the number of patients receiving ulipristal acetate is estimated to be 30 in 2013 increasing to 145 in 2017.

5.1.2 Results

The company anticipates a net cost saving from switching to ulipristal acetate from the currently used GnRHa. This is primarily driven by saving the costs of GP and hospital visits for the administration of the comparators. The results of the base case are summarised in Table 4. The impact of variations in treatment length, price of GnRHa, percentage requiring a separate appointment for hospital administration of first injection, percentage receiving first injection at GP practice, use of add-back therapy and the percentage of GPs that claim fees under DES were explored in sensitivity analyses. The results showed that the use of ulipristal acetate resulted in cost savings in all explored analyses except under the assumption that no patients would require a separate appointment to receive their first injection at hospital, where the total five year incremental cost was estimated to be £2,746.

Table 4. Company-reported costs with the use of ulipristal acetate in uterine fibroids patients prior to surgery.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication(s) covered in this submission)	337	337	337	337	337
Uptake (%)	9%	15%	21%	30%	43%
Treated patients	30	51	71	101	145
Net costs versus weighted average of GnHRas					
Medication	+£2,421	+£4,115	+£5,729	+£8,150	+£11,700
Primary care	−£2,572	−£4,373	−£6,088	−£8,660	−£12,432
Secondary and tertiary care	−£2,035	−£3,460	−£4,817	−£6,852	−£9,837
Staffing	N/A				
Infrastructure					
Personal social services					
Overall net cost	**−£2,186**	**−£3,718**	**−£5,176**	**−£7,362**	**−£10,569**

5.1.3 AWTTC critique of the budget impact analysis

- The company has made reasonable effort to characterise the epidemiology of moderate to severe uterine fibroids symptoms in Wales using data from the NHS Information Centre.
- The validity of the anticipated savings is dependent on the validity of GnRHa usage levels derived from a Welsh consultants' survey, given that comparators' costs are calculated as weighted average cost based on these estimates.

- The cost estimates are derived from the company CMA, therefore the limitations and uncertainties associated with the costs assumed in the CMA also apply to the budget impact analysis. Moreover, the net financial costs of introducing ulipristal acetate in practice may not be equivalent to the opportunity costs calculated for the economic analysis.

5.2 Table of comparative unit costs

AWTTC identified the GnRHa therapies leuprorelin acetate and goserelin acetate as the most appropriate comparators for ulipristal acetate in the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. Examples of acquisition costs for ulipristal acetate and its comparator GnRHa preparations are shown in Table 5.

Table 5. Examples of acquisition costs for pre-operative treatments of moderate to severe symptoms of uterine fibroids.

Regimen	Example dose*	Example cost per three-month treatment course**
Ulipristal acetate (Esmya®▼) Oral tablets, 5 mg	Once daily for up to three months.	£342.39
Leuprorelin acetate (Prostrap® SR DCS) Pre-filled syringe, 3.75 mg	**Uterine fibroids**, 3.75 mg as single subcutaneous or intramuscular injection every month for three to four months, max six months.	£225.72
Triptorelin acetate (Decapeptyl®) Vials, 3 mg and 11.25 mg	**Fibroids**, 3 mg by intramuscular injection every 28 days for minimum of 3 months.	£207.00
Goserelin acetate (Zoladex®) Biodegradable depot, 3.6 mg	One 3.6 mg depot subcutaneously into anterior abdominal wall every 28 days for max. six months.	£195.00
*Doses based on SPCs[2,10,16–18] **Costs are based on current MIMS list prices as of 9 February 2013[19], assuming three months of treatment. Note leuprorelin acetate and triptorelin acetate may be used for up to six months. This table does not imply therapeutic equivalence of drugs or the stated doses.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, ulipristal acetate (Esmya®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

The company do not anticipate that ulipristal acetate (Esmya®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted ongoing studies that are likely to be available within 6–12 months[1]:

- PGL09-026: Long-term efficacy of ulipristal acetate, predominantly in patients who wish to avoid fibroid surgery[20].
- PGL09-027: Extension study of PGL09-026[21].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search
Date of evidence search: 18 January 2013 and 21 January 2013
Date range of evidence search: No date limits were applied to database searches.

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