

Addendum to Clinical Guideline 44, Heavy menstrual bleeding: assessment and management

Clinical Guideline Addendum 44.1

Methods, evidence and recommendations

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1 **Clinical guidelines update**

- 2 The NICE Clinical Guidelines Update Team update discrete parts of published clinical
3 guidelines as requested by NICE's Guidance Executive.
- 4 Suitable topics for update are identified through the new surveillance programme (see
5 [surveillance programme interim guide](#)).
- 6 These guidelines are updated using a standing Committee of healthcare professionals,
7 research methodologists and lay members from a range of disciplines and localities. For the
8 duration of the update the core members of the Committee are joined by up to 5 additional
9 members who are have specific expertise in the topic being updated, hereafter referred to as
10 'topic expert members'.
- 11 In this document where 'the Committee' is referred to, this means the entire Committee, both
12 the core standing members and topic expert members.
- 13 Where 'standing committee members' is referred to, this means the core standing members
14 of the Committee only.
- 15 Where 'topic expert members' is referred to this means the recruited group of members with
16 topic expertise.
- 17 All of the core members and the topic expert members are fully voting members of the
18 Committee.
- 19 Details of the Committee membership and the NICE team can be found in appendix A. A link
20 to the Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on heavy menstrual bleeding (NICE [Clinical guideline 44](http://www.nice.org.uk/guidance/cg44/resources/heavy-menstrual-bleeding-surveillance-review-decision-march-20153)) was reviewed in 2015 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to the use of medical treatments for fibroids. The full report can be found here: <http://www.nice.org.uk/guidance/cg44/resources/heavy-menstrual-bleeding-surveillance-review-decision-march-20153>.

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer...') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.2 Recommendations

1 Women should be given the following information on potentially unwanted outcomes. [2007, amended 2016]

Treatment	Potential unwanted outcomes experienced by some women Common: 1 in 100 chance; less common: 1 in 1000 chance; rare: 1 in 10,000 chance; very rare: 1 in 100,000 chance)

Levonorgestrel-releasing intrauterine system [2007]	<p>Common: irregular bleeding that may last for over 6 months; hormone-related problems such as breast tenderness, acne or headaches, which, if present, are generally minor and transient</p> <p>Less common: amenorrhoea</p> <p>Rare: uterine perforation at the time of insertion</p>
Tranexamic acid [2007]	<p>Less common: indigestion; diarrhoea; headaches</p>
Non-steroidal anti-inflammatory drugs [2007]	<p>Common: indigestion; diarrhoea</p> <p>Rare: worsening of asthma in sensitive individuals; peptic ulcers with possible bleeding and peritonitis</p>
Combined oral contraceptives [2007]	<p>Common: mood changes; headaches; nausea; fluid retention; breast tenderness</p> <p>Very rare: deep vein thrombosis; stroke; heart attacks</p>
Oral progestogen (norethisterone) [2007]	<p>Common: weight gain; bloating; breast tenderness; headaches; acne (but all are usually minor and transient)</p> <p>Rare: depression</p>
Injected progestogen [2007]	<p>Common: weight gain; irregular bleeding; amenorrhoea; premenstrual-like syndrome (including bloating, fluid retention, breast tenderness)</p> <p>Less common: small loss of bone mineral density, largely recovered when treatment discontinued</p>
Ulipristal acetate [new 2016]	<p>Very common: endometrial thickening, amenorrhoea</p> <p>Common: vertigo, nausea, abdominal pain, hot flushes, headache, fatigue, ovarian cyst, breast pain and tenderness, pelvic pain, musculoskeletal pain, acne, weight increase</p> <p>Less common: dizziness, dry mouth, constipation, anxiety, urinary incontinence, alopecia, dry skin, hyperhidrosis, back pain, uterine haemorrhage, metrorrhagia, genital discharge, oedema, asthenia, increased blood lipids</p> <p>Rare: epistaxis, dyspepsia, flatulence, ruptured ovarian cyst, breast swelling</p>
Gonadotrophin-releasing hormone analogue [2007]	<p>Common: menopausal-like symptoms (such as hot flushes, increased sweating, vaginal dryness)</p> <p>Less common: osteoporosis, particularly trabecular bone with longer than 6-months' use</p>
Endometrial ablation [2007]	<p>Common: vaginal discharge; increased period pain or cramping (even if no further bleeding); need for additional surgery</p>

	<p>Less common: infection</p> <p>Rare: perforation (but very rare with second generation techniques)</p>
Uterine artery embolisation [2007]	<p>Common: persistent vaginal discharge; post-embolisation syndrome – pain, nausea, vomiting and fever (not involving hospitalisation)</p> <p>Less common: need for additional surgery; premature ovarian failure particularly in women over 45 years old; haematoma</p> <p>Rare: haemorrhage; non-target embolisation causing tissue necrosis; infection causing septicaemia</p>
Myomectomy [2007]	<p>Less common: adhesions (which may lead to pain and/or impaired fertility); need for additional surgery; recurrence of fibroids; perforation (hysteroscopic route); infection</p> <p>Rare: haemorrhage</p>
Hysterectomy [2007]	<p>Common: infection</p> <p>Less common: intraoperative haemorrhage; damage to other abdominal organs, such as the urinary tract or bowel; urinary dysfunction – frequent passing of urine and incontinence</p> <p>Rare: thrombosis (DVT and clot on the lung)</p> <p>Very rare: death</p> <p>(Complications are more likely when hysterectomy is performed in the presence of fibroids.)</p>
Oophorectomy at time of hysterectomy [2007]	<p>Common: menopausal-like symptoms</p>

2 Offer ulipristal acetate 5 mg (up to 4 courses)¹ to women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level of 102 g per litre or below. [new 2016]

3 Consider ulipristal acetate 5 mg (up to 4 courses)² for women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level above 102 g per litre. [new 2016]

¹ The summary of product characteristics states: 'In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period.'

² The summary of product characteristics states: 'In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period.'

1.31 Patient-centred care

- 2 This addendum to the [NICE clinical guideline on heavy menstrual bleeding](#) offers best
3 practice advice on the treatment of women of reproductive age with uterine fibroids of 3 cm
4 or more.
- 5 Patients and healthcare professionals have rights and responsibilities as set out in the [NHS](#)
6 [Constitution for England](#) – all NICE guidance is written to reflect these. Treatment and care
7 should take into account individual needs and preferences. Patients should have the
8 opportunity to make informed decisions about their care and treatment, in partnership with
9 their healthcare professionals. Healthcare professionals should follow the [Department of](#)
10 [Health's advice on consent](#). If someone does not have the capacity to make decisions,
11 healthcare professionals should follow the [code of practice that accompanies the Mental](#)
12 [Capacity Act](#) and the supplementary [code of practice on deprivation of liberty safeguards](#). In
13 Wales, healthcare professionals should follow advice on consent from the Welsh
14 Government.
- 15 NICE has produced guidance on the components of good patient experience in adult NHS
16 services. All healthcare professionals should follow the recommendations in [Patient](#)
17 [experience in adult NHS services](#).

1.48 Methods

- 19 This update was developed based on the process and methods described in the [guidelines](#)
20 [manual 2014](#).

2₁ Evidence review and recommendations

2.1₂ Introduction

3 The NICE guideline on heavy menstrual bleeding was reviewed in 2015, and new evidence
4 on the effectiveness of progesterone receptor modulators for the treatment of uterine fibroids
5 of 3 cm or more was found. The aim of the review was to evaluate the effectiveness of
6 progesterone receptor modulators compared with placebo and other pharmaceutical
7 treatments for fibroids in women of reproductive age with fibroids of 3 cm or more in
8 diameter.

2.2₉ Review question

10 What is the clinical and cost effectiveness of medical treatment with progesterone receptor
11 modulators for fibroids greater than 3 cm in diameter?

2.3₂ Clinical evidence review

2.3.1₃ Methods and results

14 A systematic review of the literature was conducted, as specified in the review protocol in
15 Appendix C. The protocol was developed in consultation with the topic expert members, and
16 then reviewed by the core Committee members, before the review was carried out. The
17 following outcomes were considered important for decision making: quality of life (total score
18 and symptom subscales), menstrual blood loss, fibroid volume, uterine volume, bone mineral
19 density, endometrial hyperplasia and preservation of fertility (measured as the number of
20 women conceiving after treatment, and the number of women with a regular menstrual cycle
21 after treatment). The number of participants undergoing a surgical/radiological procedure
22 was also included as a post-hoc additional outcome in the protocol, at the request of the
23 Committee.

24 A systematic search (see appendix D) identified 684 articles. The titles and abstracts were
25 screened and 44 articles were identified as potentially relevant. Full-text versions of these
26 articles were obtained and reviewed against the criteria specified in the review protocol
27 (appendix C). Of these, 26 were excluded as they did not meet the criteria and 18 met the
28 criteria and were included. Of the identified articles, 3 were additional reports of a study that
29 was already included, leaving 15 included studies.

30 A review flowchart is provided in appendix E, and the excluded studies (with reasons for
31 exclusion) are shown in appendix F.

32 For a summary of included studies see Table 1 (for the full evidence tables and full GRADE
33 profiles please see appendices G and H). Evidence was found on the following comparisons:

- 34 • Mifepristone (5, 10 or 25mg/d) vs Placebo
- 35 • Mifepristone 2.5mg/d vs Mifepristone 5mg/d
- 36 • Mifepristone 5mg/d vs Mifepristone 10mg/d
- 37 • Mifepristone 10mg/d vs Mifepristone 25mg/d
- 38 • Ulipristal acetate vs Placebo
- 39 • Ulipristal acetate vs Leuporelin acetate (also known as Leuprolide acetate)
- 40 • Ulipristal acetate 5mg/d vs Ulipristal acetate 10mg/d

41 When more than one study assessed an outcome for a given comparison, data were
42 combined using pair-wise meta-analyses. The Mantel-Haenszel and inverse variance

1 methods were used for dichotomous and continuous outcomes, respectively. The I^2 , χ^2 and
2 τ^2 statistics were calculated to assess heterogeneity. Forest plots showing the outcome of
3 these meta-analyses are shown in appendix I. A fixed effects model was used when
4 comparisons were made for the same medicine and dose (e.g. mifepristone 5mg vs
5 mifepristone 10mg) unless substantial unexplained heterogeneity was found, (I^2 value > 50%
6 and no explanation for heterogeneity found based on differences in population or study
7 design). A random effects model was chosen when different doses of medicine were
8 combined in the same analysis (e.g. mifepristone (all doses) vs placebo), because the
9 treatment effects were unlikely to be identical across studies. The studies comparing
10 ulipristal acetate with placebo and leuporelin acetate had 2 groups assigned to ulipristal
11 acetate; 1 taking ulipristal acetate 5mg and 1 taking ulipristal acetate 10mg. For the purpose
12 of analysis, the 5mg/d group data were used as this dose corresponds to the dose specified
13 in the summary of product characteristics for this medicine.

14 Many of the outcomes for the review were reported as change measures from baseline (for
15 example, change in menstrual blood loss or uterine volume). Some studies did not report this
16 measure directly, but instead reported the measure at baseline and at follow up for each
17 group. Change from baseline measures were used in the analysis where available, as they
18 are generally more precise as they take into account the correlation between baseline and
19 endpoint measures. When change from baseline measures were not reported, endpoint
20 measures were used in the analysis. Where both baseline and change from baseline
21 measures were reported for an outcome, they were analysed separately as outcome
22 subgroups and also combined in a meta-analysis.

23 Data were not available to assess any of the subgroup effects specified in the review
24 protocol (fibroid volume 3 cm or more, single vs multiple fibroids, fibroid location, pre-surgical
25 vs definitive treatment).

26 The quality of evidence for each outcome for each comparison was appraised using the
27 approach recommended by the Grading of Recommendations, Assessment, Development
28 and Evaluation (GRADE) working group (for full GRADE profiles, see appendix H). All
29 included studies were randomised controlled trials. Risk of bias was assessed by considering
30 whether there were serious or very serious limitations in study design in the studies that
31 contributed to each outcome. Typical reasons that outcomes were judged to have serious
32 risk of bias included an imbalance in the number of dropouts across groups, poorly matched
33 baseline characteristics across groups or a lack of blinding of participants or investigators.
34 Outcomes were judged to have very serious risk of bias if the contributing studies had
35 multiple methodological limitations or limitations that very seriously impacted the study
36 design.

37 Inconsistency (the variability in the results from different trials) was only assessed when data
38 were combined in a meta-analysis. The degree of heterogeneity was assessed, and 95%
39 confidence intervals were examined to determine whether serious inconsistency was
40 present, using the methods described by the GRADE working group. Indirectness was
41 assessed by noting whether the evidence directly applied to the review question; the
42 outcome 'endometrial thickness' was judged to have serious indirectness because it was a
43 surrogate measure for endometrial hyperplasia. Imprecision was assessed by determining
44 whether 95% confidence intervals incorporated clinically important harm, no effect and
45 clinically important benefit. If all three were incorporated in the confidence interval,
46 imprecision was judged very serious. If two of the three were incorporated, imprecision was
47 considered serious. Other factors such as publication bias were also considered, but none
48 gave rise to serious uncertainty.

49 The GRADE default minimally important differences were used (0.75 and 1.25 for
50 dichotomous outcomes, and -0.5 and 0.5 standardised mean differences for continuous
51 outcomes). Published minimally important differences were sought for all outcomes via an
52 internet search and through consulting the topic expert members, but none were found.

1 Table 1: Summary of included studies

Study id	Population	Intervention & comparator	Location and setting	Outcomes reported
Mifepristone vs Placebo				
Bagaria 2009	Premenopausal women with symptomatic fibroids	Mifepristone 10mg vs Placebo	India, secondary care	Fibroid volume, uterine volume
Engman 2009	Women with symptomatic fibroids requiring surgery	Mifepristone 25mg vs Placebo	Sweden, secondary care	Menstrual blood loss (data not usable in analysis), fibroid volume, uterine hyperplasia
Esteve 2013	Women of reproductive age with symptomatic fibroids requiring surgery	Mifepristone 5mg vs Placebo	Cuba, secondary care	Quality of life, fibroid volume, uterine volume, uterine thickness (surrogate for uterine hyperplasia)
Fiscella 2006	Premenopausal women with symptomatic fibroids and uterine volume > 160 cm ³	Mifepristone 5mg vs Placebo	USA secondary care	Quality of life, menstrual blood loss, uterine volume
Mifepristone vs Leuporelin acetate				
Reinsch 1994	Women scheduled for hysterectomy or myomectomy	Mifepristone 25mg vs Leuporelin acetate	USA secondary care	Uterine volume (data not usable in analysis)
Mifepristone (dose 1) vs Mifepristone (dose 2)				
Carbonell 2012	Women of reproductive age with symptomatic fibroids requiring surgery	Mifepristone 2.5mg vs Mifepristone 5mg	Cuba and Nicaragua, secondary care	Fibroid volume, uterine volume, endometrial hyperplasia
Carbonell 2013a	Women of reproductive age with symptomatic fibroids	Mifepristone 2.5mg vs Mifepristone 5mg	Cuba, secondary care	Fibroid volume, uterine volume, endometrial thickness (surrogate for uterine hyperplasia)
Carbonell 2008	Women of reproductive age with symptomatic fibroids	Mifepristone 5mg vs Mifepristone 10mg	Cuba, secondary care	Fibroid volume, uterine volume
Esteve 2012	Women of reproductive age with symptomatic fibroids	Mifepristone 5mg vs Mifepristone 10mg	Cuba, secondary care	Fibroid volume, uterine volume, endometrial thickness (surrogate for uterine hyperplasia)
Carbonell 2013b	Women of reproductive age with symptomatic fibroids	Mifepristone 5mg vs Mifepristone 10mg	Cuba, secondary care	Quality of life, fibroid volume, uterine volume, endometrial hyperplasia, endometrial thickness (surrogate for uterine hyperplasia)
Eisinger 2003	Premenopausal women with symptomatic fibroids and	Mifepristone 5mg vs Mifepristone 10mg	USA, secondary care	Menstrual blood loss, uterine volume, uterine hyperplasia, (surrogate for uterine hyperplasia)

	uterine volume > 300 cm ³			
Kulshrestha 2013	Women of reproductive age with symptomatic fibroids > 5cm diameter	Mifepristone 10mg vs Mifepristone 25mg	India, secondary care	Fibroid volume (data not useable in analysis) , endometrial hyperplasia, endometrial thickness
Ulipristal acetate vs Placebo				
Donnez 2012a	Women of reproductive age with symptomatic fibroids of at least 3 cm diameter requiring surgery	Ulipristal acetate (1 course of 5 or 10mg/d) vs Placebo	International (38 centres), research centres	Menstrual blood loss, fibroid volume, uterine volume, endometrial hyperplasia, endometrial thickness (surrogate for uterine hyperplasia), number of participants undergoing surgical/radiological procedure
Ulipristal acetate vs Leuprorelin acetate				
Donnez 2012b	Women of reproductive age with symptomatic fibroids of at least 3 cm diameter requiring surgery	Ulipristal acetate (1 course of 5 or 10mg/d) vs Leuprorelin acetate	International (multicentre), research centres	Quality of life, menstrual blood loss, fibroid volume, uterine volume, endometrial hyperplasia, endometrial thickness (surrogate for uterine hyperplasia), number of participants undergoing surgical/radiological procedure
Ulipristal acetate 5mg vs Ulipristal acetate 10mg				
Donnez 2015	Women of reproductive age with symptomatic fibroids of at least 3 cm diameter	Ulipristal acetate 5mg (4 courses) vs Ulipristal acetate 10mg (4 courses)	International (46 centres), research centres	Quality of life, menstrual blood loss, fibroid volume, uterine volume, endometrial hyperplasia, endometrial thickness (surrogate for uterine hyperplasia)

2.4.1 Health economic evidence review

2.4.12 Methods

3 Evidence of cost effectiveness

4 The Committee is required to make decisions based on the best available evidence of both
5 clinical and cost effectiveness. Guideline recommendations should be based on the expected
6 costs of the different options in relation to their expected health benefits rather than the total
7 implementation cost.

8 Evidence on cost effectiveness related to the key clinical issues being addressed in the
9 guideline update was sought. The health economist undertook a systematic review of the
10 published economic literature.

11 Economic literature search

12 A systematic literature search was undertaken to identify health economic evidence within
13 published literature relevant to the review questions. The evidence was identified by
14 conducting a broad search relating to progesterone receptor modulators for heavy menstrual
15 bleeding in the NHS Economic Evaluation Database (NHS EED) and the Health Technology
16 Assessment database (HTA). The search also included Medline and Embase databases
17 using an economic filter. Studies published in languages other than English were not
18 reviewed. The search was conducted on 22.09.2015. The health economic search strategies
19 are detailed in appendix J.

20 The health economist also sought out relevant studies identified by the surveillance review or
21 Committee members.

22 Economic literature review

23 The health economist:

- 24 • Identified potentially relevant studies for the review question from the economic search
25 results by reviewing titles and abstracts. Full papers were then obtained.
- 26 • Reviewed full papers against pre-specified inclusion and exclusion criteria to identify
27 relevant studies.

28 Inclusion and Exclusion criteria

29 Full economic evaluations (studies comparing costs and health consequences of alternative
30 courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence
31 analyses) and comparative costing studies that address the review question in the relevant
32 population were considered potentially includable as economic evidence.

33 Studies that only reported burden of disease or cost of illness were excluded. Literature
34 reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and
35 studies not in English were excluded.

36 Remaining studies were prioritised for inclusion based on their relative applicability to the
37 development of this guideline and the study limitations. For example, if a high quality, directly
38 applicable UK analysis was available, then other less relevant studies may not have been
39 included. Where selective exclusions occurred on this basis, this is noted in the excluded
40 economic studies table (appendix L).

1 For more details about the assessment of applicability and methodological quality see the
2 economic evaluation checklist contained in *Appendix H of Developing NICE Guidelines: the*
3 *manual 2014*.

4 **Undertaking de novo health economic modelling**

5 As well as reviewing the published economic literature, de novo health economic modelling
6 was undertaken by the health economist.

7 The following general principles were adhered to in developing the cost-effectiveness
8 analysis:

- 9 • Methods were consistent with the NICE reference case.
- 10 • The Committee was involved in the design of the model, selection of inputs and
11 interpretation of results.
- 12 • Model inputs were based on the systematic review of the clinical literature supplemented
13 with other published data sources where possible.
- 14 • When published data were not available, Committee expert opinion was used to populate
15 the model.
- 16 • Model inputs and assumptions were reported fully and transparently.
- 17 • The results were subject to sensitivity analysis and limitations were discussed.
- 18 • The model was quality assured by another health economist within NICE's Centre for
19 Clinical Practice.

20 Full methods and results for the cost-effectiveness analysis conducted for this guideline
21 update are described in Appendix M.

2.4.22 **Results of the economic literature review**

23 The search returned 138 articles. 135 of these were excluded based on title and abstract.
24 Full papers were obtained for 3 articles. All studies were subsequently excluded.

25 The flowchart summarising the number of studies included and excluded at each stage of the
26 review process can be found in appendix K. Appendix L contains a list of excluded studies
27 and the reason for their exclusion.

2.4.38 **De novo economic modelling**

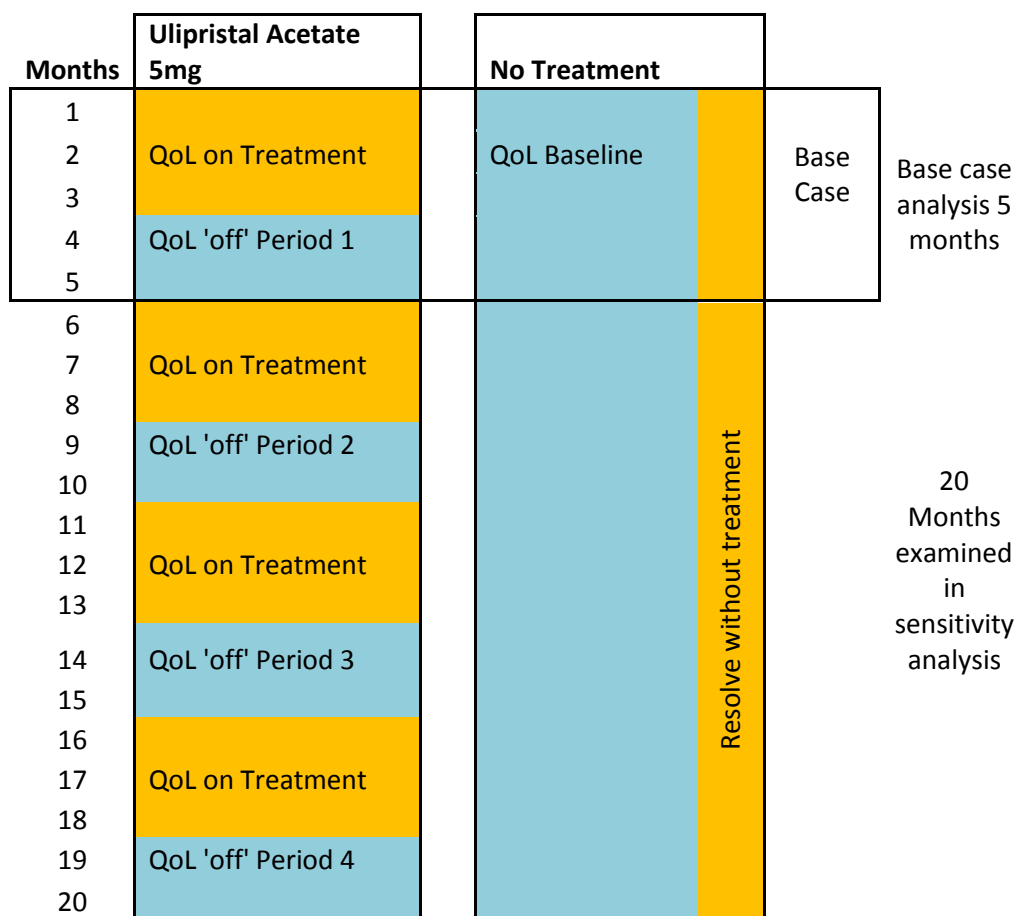
29 The modelling originally conducted for CG44 was not used in this update as it was not
30 suitable as no data on fibroids of 3 cm or more were included.

31 De novo health economic modelling was undertaken for this update. The decision model
32 compared 3 months of treatment with ulipristal acetate 5mg followed by a 2 month period off
33 treatment with 5 months of no treatment. The time horizon was extended to 20 months in
34 sensitivity analysis to examine the cost effectiveness of repeated courses of treatment. The
35 committee noted that there was some uncertainty in the average 'off treatment' time so a 1
36 month 'off treatment' period was also examined. In line with the trial evidence, symptoms
37 were assumed to resolve in a proportion of patients in the 'no treatment' arm. The
38 effectiveness of the intervention was modelled as the difference in health related quality of
39 life between women on and off treatment. These quality of life values calculated using an
40 equation that linked levels pain and blood loss reported in the trials to EQ-5D scores in the
41 base case although a variety of other plausible values were obtained from the literature and
42 examined in sensitivity analysis. Diagram 1 shows a diagram of the model.

43

1 Diagram 1: Diagram of the economic model

2



3

4

5 Please refer to Appendix M for the full details of this analysis.

2.4.46 Unit costs

7 Unit costs of leuprorelin acetate and ulipristal acetate are provided in Table 2. Mifepristone
8 appears to only be available as 200mg tablets in the UK. The doses used in clinical trials
9 range from 2.5mg to 25mg per day. Therefore, an accurate cost of mifepristone as it would
10 be used for heavy menstrual bleeding in clinical practice in the UK could not be established.

11 Standard unit costs for NHS resources such as consultant visits and ultrasound scans were
12 taken from national schedules of costs. See Appendix M for details.

13 **Table 2: Unit costs of a gonadotrophin-releasing hormone analogue and**
14 **progesterone receptor modulators**

Medicine	Dose	Price per pack (£)	Doses per pack	Cost per dose (£)	Cost for 3 month course (£)	Source
Leuprorelin acetate 3.75mg/month (Prostap SR DCS (Takeda));	3.75mg injection once per month plus £8.50 x 3 for the staff cost of	75.24	1	75.24	251.22	Drug cost: Drug Tariff; Staff cost: PSSRU Unit

Medicine	Dose	Price per pack (£)	Doses per pack	Cost per dose (£)	Cost for 3 month course (£)	Source
gonadotrophin-releasing hormone analogue)	administration based on 15 minutes of hospital nurse, day ward					Costs of Health and Social Care 2014
Ulipristal acetate 5mg/day (Esmya (Gedeon Richter); progesterone receptor modulator)	5mg tablet per day for 3 months (licensed dose of ulipristal acetate)	114.13	28	4.08	342.39	BNF online 28 October 2015

2.5.1 Evidence statements

2.5.1.2 Clinical evidence statements

3 Four studies (236 participants) compared mifepristone with placebo for the treatment of
4 fibroids. Treatment durations were 3 to 6 months. Moderate to very low quality evidence
5 from two studies (42 and 124 participants) favoured mifepristone in terms of quality of life,
6 although there was substantial heterogeneity between studies. Moderate quality evidence
7 from a single small study (42 participants) favoured mifepristone in terms of menstrual blood
8 loss. Low quality evidence on fibroid and uterine volume was less clear, with some evidence
9 favouring mifepristone, but with uncertain clinical importance. Very low quality evidence from
10 a single study (105 participants) on endometrial thickness (a surrogate measure for uterine
11 hyperplasia) favoured placebo (MD =1.9mm, 95% CI: 0.8 to 3.0).

12 Seven studies (902 participants) compared doses of mifepristone (2.5 to 25mg/d) for the
13 treatment of fibroids. There was no clear evidence favouring one dose over another across
14 any of the dose comparisons.

15 One study (144 participants) compared ulipristal acetate (5mg/d) with placebo (treatment
16 duration 3 months). High quality evidence favoured ulipristal acetate over placebo in terms of
17 menstrual blood loss (median difference=-291 pictorial blood loss index units, -399 to -194).
18 Moderate quality evidence also favoured ulipristal acetate in terms of fibroid volume, but the
19 difference was of uncertain clinical importance. Low quality evidence on endometrial
20 hyperplasia was inconclusive, and there was moderate quality evidence suggesting no
21 difference in endometrial thickness between ulipristal acetate and placebo. Low quality
22 evidence on the number of participants undergoing a surgical/radiological procedure was
23 inconclusive.

24 One study (199 participants) compared ulipristal acetate (5mg/d) with the gonadotrophin
25 releasing hormone analogue leuprorelin acetate (treatment duration 3 months). There was
26 high quality evidence of no clinically important difference in quality of life and menstrual blood
27 loss between treatments. There was moderate quality evidence for no clinically important
28 difference in the volume of the 3 largest fibroids across treatments, but high quality evidence
29 showing clinically important difference in uterine volume favouring leuprorelin acetate (risk
30 ratio of ulipristal acetate relative to leuprorelin acetate = 1.48, 95% CI: 1.3 to 1.7, moderate
31 quality). The evidence on endometrial hyperplasia was inconclusive, and there was moderate
32 quality evidence favouring leuprorelin acetate on endometrial thickness at 3 months follow-up
33 but there was moderate quality evidence for no difference in endometrial thickness between
34 ulipristal acetate and leuprorelin acetate at 6 months after the end of treatment. Moderate
35 quality evidence on the number of participants undergoing a surgical/radiological procedure
36 after the end of 13 weeks ulipristal acetate treatment suggested no difference between
37 groups.

- 1 One study compared doses of ulipristal acetate (5mg/d vs 10mg/d). There was no evidence
- 2 of a clinically important difference between doses for any of the reported outcomes.

2.5.23 Health economic evidence statements

- 4 No studies were included in the economic evidence review.
- 5 The results of an original health economic model built for this guideline found ulipristal
- 6 acetate to be cost effective compared to standard care. This analysis was assessed as
- 7 directly applicable with minor limitations.

2.68 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	<p>The committee selected quality of life as a critical outcome for decision making because it incorporates the impact of symptom changes and gives the best estimate of the effects of fibroids on a women's everyday activities and lifestyle. Uterine volume and menstrual blood loss were also considered to be critical outcomes because menstrual blood loss is often the primary complaint of women with fibroids and uterine volume was likely to determine pressure-related urinary and bowel symptoms which are also important to many women. The committee noted that the retention of the uterus and thus fertility may be very important for some women and less important for others, and this may depend on whether a women wishes to have children in the future. Endometrial hyperplasia was considered an important safety outcome, because of its link to endometrial cancer. However, the topic experts noted that the changes produced by UPA are not hyperplasia as such and are known as progesterone receptor modulator associated endometrial changes (PAEC) and are specific to this group of drugs. Endometrial hyperplasia is rare although it has been reported with other members of the same class of drugs, and therefore differences in endometrial hyperplasia rates between treatments were unlikely to be detected in short-term randomised controlled trials.</p>
Quality of evidence	<p>Four small studies compared mifepristone with placebo. For this comparison, menstrual blood loss and quality of life were only reported by 1 and 2 studies, respectively. The effect of mifepristone on quality of life was associated with serious unexplained heterogeneity (with 1 small study favouring mifepristone and another study suggesting no difference between mifepristone and placebo). This limited certainty in the evidence for mifepristone compared with placebo. There were 2 large multicentre studies comparing ulipristal acetate with placebo and leuprorelin acetate, respectively. Both studies were funded and carried out by the manufacturer of ulipristal acetate. These studies appeared to be generally well conducted, and results for most outcomes were precise. However, it was not possible to assess inconsistency for each outcome as only a single study was available for each comparison.</p> <p>Evidence on endometrial hyperplasia was inconclusive across the evidence base, with few events per group and very wide confidence intervals. The committee acknowledged that short-term randomised controlled trials were unlikely to be suitable for detecting differences in rates of endometrial hyperplasia between treatments because it is rare (although potentially very serious). Endometrial thickness was considered as an indirect surrogate measure of hyperplasia, as endometrial hyperplasia is almost always preceded by thickening of the endometrium.</p> <p>When considering ulipristal acetate the committee accepted that data (rated as high quality) were only available for the following one critical outcome, menstrual blood loss measured using a pictorial blood-loss assessment</p>

	Committee discussions
	<p>chart (PBAC) Other important outcomes were assessed as between moderate and very low quality. The committee also noted that the evidence does not show that ulipristal acetate reduces the need for hysterectomy in women with heavy menstrual bleeding.</p> <p>The committee expressed concern that the majority of data comparing ulipristal acetate with placebo and leuprorelin acetate was from short-term studies (3 months treatment) and the data on both longer term effectiveness and more than one cycle of treatment were less and also of lower quality. For example, it was noted that ulipristal acetate was not associated with a reduction in surgery rates after 13 weeks of treatment (although reduced surgery rates were not an aim of treatment in the study as only 18 women out of 451 underwent surgery in one study), and there was no evidence on surgery rates after more than one treatment cycle. There is also a paucity of safety data either of ulipristal acetate beyond the 4 courses of treatment examined in the included studies or any long-term adverse effects of up to 4 courses of treatment with ulipristal acetate.</p> <p>Concerns were raised regarding the generalisability of the populations in the included studies to the wider population of women with heavy menstrual bleeding. This concern was particularly acute for trials examining ulipristal acetate included in the clinical and economic model as these were carried out in very selective populations of women with moderate to severe heavy menstrual bleeding. For example, including women who were considering surgery and women who were anaemic (haemoglobin level 102 g per litre or less) which is a subset of all women with fibroids and heavy menstrual bleeding. The committee noted that this haemoglobin level was an inclusion criteria in the only included study that assessed the clinical effectiveness of ulipristal acetate versus placebo. It was also noted that haemoglobin level can be improved by various factors, including iron supplementation, and also that haemoglobin levels may be higher in some women with heavy menstrual bleeding seen in clinical practice..</p> <p>It was noted that the PBAC is not frequently used in UK clinical practice and clinicians assess heavy menstrual bleeding by clinical history supported by other investigations (including laboratory, structural and histological). Therefore, method of assessment of outcomes in the studies may not be relevant to UK clinical practice. It was also noted that a woman's self-reported symptom status is key to assessing severity of symptoms and subsequent treatment options and decisions. The original guideline (CG44) was largely based on patient perception of symptoms and the committee accepted that these are subjective and no objective measurement of the symptoms was available. The committee noted that if a woman says she is experiencing HMB then it is likely that it is impacting significantly on quality of life. The committee were mindful of the fact the Summary of Product Characteristics does not quantify or define moderate to severe symptoms. The committee agreed that these level of symptoms likely relate to the included participants in trials of ulipristal acetate conducted and took account of the fact that one of the included studies used anaemia (<102 g per litre) as an inclusion criteria. The topic experts noted that the evidence in these studies reflected their own clinical experience. The committee agreed that it was important to have separate recommendations to reflect the strong evidence base covering women with heavy menstrual bleeding and fibroids of 3 cm or more and with anaemia and drafted an 'offer' recommendation for the use of 5mg ulipristal acetate to women with heavy menstrual bleeding and fibroids of 3 cm or more and with anaemia (a haemoglobin level of 102 g per litre or below)</p> <p>The committee then reflected on</p>

	Committee discussions
	<ul style="list-style-type: none"> ○ the concerns surrounding the generalisability of the evidence to clinical practice ○ the fact that women with anaemia will be offered iron and that, over time, their haemoglobin levels will increase above the cut-off 102 g per litre specified in the recommendation ○ there was no strong evidence of harm associated with 5mg ulipristal acetate <p>and to draft a 'consider' recommendation for the use of 5mg ulipristal acetate to women with heavy menstrual bleeding and fibroids of 3 cm or more who do not have anaemia.as it was considered likely that these women will benefit access to this treatment.</p>
Trade-off between benefits and harms	<p>The committee agreed that overall the evidence favoured both mifepristone and ulipristal acetate over placebo, although the evidence favouring mifepristone was mainly based on a single trial and was very limited. Evidence on the long-term effectiveness of ulipristal acetate was uncertain because of the lack of evidence on benefits and harms of multiple treatment (more than 4) cycles. Evidence comparing mifepristone and leuporelin acetate was inconclusive, with only a single study that did not report outcomes that could be analysed as a range (rather than a confidence interval or standard deviation) was reported. Ulipristal acetate and leuporelin acetate were similar in effectiveness in terms of quality of life and menstrual blood loss, and there was evidence that favoured leuporelin acetate over ulipristal acetate in terms of uterine volume. Both treatments were associated with a large decrease in menstrual blood loss, which the topic experts advised would be valued highly by women with fibroids. The topic experts also noted that ulipristal acetate is delivered orally, whereas leuporelin is delivered by injection by a healthcare professional. The topic experts noted that women may prefer an oral route of administration. The committee considered that gonadotrophin releasing hormone analogues were more suitable for pre-surgical treatment than ulipristal acetate, when reduction in uterine volume is important to facilitate surgery. This is consistent with the current NICE recommendation to offer gonadotrophin releasing hormones before hysterectomy or myomectomy if the uterus is large or distorted.</p> <p>The committee agreed that no difference between ulipristal acetate 5 mg or 10 mg was found and noted that 5mg daily is the licensed dosage. Therefore, they agreed to base all decisions on 5 mg dosage due to lower reported side effects and cost. However, the committee noted that there is an ongoing trial (the UCON trial) to examine the effectiveness of ulipristal acetate in women with heavy menstrual bleeding and fibroids of any size.</p> <p>The committee raised concerns that the included trials used 4 courses (20 months) of ulipristal acetate 5mg and as such, the safety of ulipristal acetate over a longer duration could not be determined even at the lower dose. However, while the committee noted that there is an ongoing trial (the UCON trial) to examine the effectiveness of UPA compared with the Mirena intra-uterine system, in women with heavy menstrual bleeding with and without fibroids. The committee decided to err on the side of caution and agreed to recommend 5mg ulipristal acetate for up to 4 courses based on efficacy and safety data from the included studies. The topic experts suggested that if a woman was in her 40's, then 5mg ulipristal acetate used intermittently would be useful as a treatment option up to the menopause. However, a woman in her 20's with moderate to severe symptoms may seek more definitive treatment as an alternative of up to 20 years of medical treatment with ulipristal acetate. The committee were also mindful of the lack of information (evidence-based or anecdotal) on long-term adverse effects of progesterone receptor modulator such as ulipristal acetate. The</p>

	Committee discussions
	<p>topic experts considered the theoretical risk of rare adverse effects by extrapolating from their knowledge of long-term adverse effects associated with estrogen-based interventions. Therefore, the committee formulated a research recommendation to address the efficacy and safety of prolonged use of ulipristal acetate for duration of more than 4 courses (20 months). However, the committee noted that there is an ongoing trial (the UCON trial) to examine the effectiveness of ulipristal acetate compared with the Mirena intra-uterine system in women.</p>
Trade-off between net health benefits and resource use	<p>No economic studies were identified in the systematic review. Therefore it was decided that economic modelling was required to determine the cost effectiveness of ulipristal acetate as a treatment for heavy menstrual bleeding in women with fibroids of 3 cm or more. Products which are not licensed for the treatment of uterine fibroids (for example, mifepristone) were not assessed. Additionally, leuprorelin acetate was not assessed as it is licensed for the pre-surgical treatment of uterine fibroids, while ulipristal acetate is licensed for pre-surgical and longer-term intermittent treatment.</p> <p>The committee noted that the model found ulipristal acetate well within the bounds of NICE's cost effectiveness threshold with a base case ICER of £10,183 per QALY gained compared to no treatment. The committee noted that the effectiveness was largely driven by the differences in utility between people on treatment and off treatment. Uncertainty existed around which utility values to use in the economic model. The base case used utility values derived from an algorithm (EQ-5D mapping algorithm) relating the pain and blood loss outcomes reported in the clinical data to Health Related Quality of Life scores. The committee noted that while there was some uncertainty inherent in using this method, no directly reported EQ-5D values for patients being treated with ulipristal acetate were available, and the results of the model were robust to sensitivity analysis using a range of possible utility values, including those assumed in the original guideline.</p> <p>The committee was not able to quantify the exact difference in consultant visits or GP appointments between the treatment pathways but noted that the results of the model were quite insensitive to plausible differences in the use of these resources due to the comparatively high utility gain in patients taking ulipristal acetate. The committee also noted that there may be some 'hidden' benefits if treatment is successful resulting in fewer GP visits but there were no data to back this up.</p> <p>The committee noted that the results of the model were also robust with respect to statistical uncertainty (as assessed by probabilistic sensitivity analysis), including that associated with the EQ-5D mapping algorithm that had been used to assign utility values. They discussed the applicability of the trial population and were concerned that the severity of symptoms, and therefore the effectiveness and cost-effectiveness of treatment with ulipristal acetate would not be the same in the average patient presenting to health services in the UK. The committee agreed that the rates of spontaneous resolution of symptoms used in the model (taken from the included studies) may be higher than those noted in clinical practice and noted that symptom severity, as measured by PBAC, was lower in patients in the Pearl IV data used in the model than in patients in the Pearl I trial presented in the clinical review and as such ulipristal acetate could be even more cost-effective.</p> <p>The committee noted that recommending ulipristal acetate within its licenced indication would likely lead to an increase in resource use due to the costs of the drug and additional appointments with healthcare professionals. The decision to assess only the 5mg preparation within the economic model had been made a priori based the fact that only this</p>

	Committee discussions
	<p>preparation had a UK licence as well as on the results of the clinical review finding no evidence of difference in effectiveness between the 5mg and 10mg preparations. The results of the economic model suggest that if the 10mg dose were assessed, there would be considerable doubt about whether the results of the model would be cost effective and robust to sensitivity analysis. This is because the cost of ulipristal acetate is the main driver of costs in the model.</p> <p>It was not possible to quantify the number of women per year in the UK with HMB and large fibroids with and without anaemia who would not be considering treatment with surgical or radiological procedures. HMB is common, however, and anaemia is common in those with the condition. These recommendations may, therefore, be associated with a moderate resource impact, though the predicted cost impact may reduce in future if prescription and monitoring become routine in primary care once more clinicians have become familiar with UPA</p>
Other considerations	<p>At the time of publication, mifepristone did not have a UK marketing authorisation for the treatment of uterine fibroids. Leuporelin acetate has a marketing authorisation for pre-surgical treatment, and ulipristal acetate has a marketing authorisation for pre-surgical and longer-term intermittent treatment. NICE is therefore only permitted to recommend mifepristone above licensed alternatives if there is good evidence of superior clinical effectiveness. Based on the current review, the committee considered that this criterion was not met and no recommendation on mifepristone was made.</p> <p>The committee also noted the license for ulipristal acetate makes no reference to women with uterine fibroids and anaemia (see http://www.medicines.org.uk/emc/) though reference is made to moderate to severe symptoms of uterine fibroids. With this consideration in mind, the committee drafted 2 recommendations for the use of ulipristal acetate 5mg for with heavy menstrual bleeding and fibroids of 3 cm or more, stratified by haemoglobin level. A row has been added to the table in recommendation 1.3.4 that includes information about the potential unwanted outcomes for ulipristal acetate (see [new 2016] row in recommendation 1.3.4) to provide information on each intervention in a single recommendation. However the committee were in agreement on the assumption that prescribers will use a drug's summary of product characteristics to inform decisions made with individual women.</p> <p>It was noted that some primary care settings formulate a traffic light classification to determine which treatments could be offered for a condition. This classification (red, amber or green) is used to define at which care setting, i.e. primary or secondary care, a treatment can be prescribed and is based on information present in the British National Formulary and NICE guidance. Ulipristal acetate is commonly given a simple amber classification, meaning women with heavy menstrual bleeding are eligible to receive ulipristal acetate as a pre-operative treatment for fibroids, on specialist advice, for a treatment period of 3 months and further follow-up).</p> <p>The committee felt it is important to highlight the varying practice in primary care as women are likely to be referred to a consultant to perform ultrasound scans and specialist investigations. In these cases, women may be placed on a waiting list prior to receiving appropriate investigations and treatment options, which may exacerbate their condition by increasing their risk of developing anaemia and other adverse conditions though anaemia is relatively uncommon where women are prescribed iron. It was noted that it may not be necessary to refer women to consultants for ultrasound scans</p>

	Committee discussions
	<p>and other investigations as these can be ordered in the general practice surgery, reducing time taken for women to receive appropriate investigations. Though it was noted that most women with fibroids requiring treatment need to be and are referred in order to get a thorough discussion of all treatment options. GPs can order them to confirm this but it is very rare for them to be familiar with the full range of treatment options.</p> <p>The Committee acknowledged that having heavy menstrual bleeding has implications on the woman's physical health and quality of life. It was noted that many women who have heavy menstrual bleeding, particularly those who would like to preserve their fertility, do not consider surgery or consider surgery as a last treatment option. The Committee agreed that all treatment options, including ulipristal acetate, other medications, radiological and surgery, should always be discussed with women. This is because recommendations to ensure women are provided with full information about treatment options are covered in various other recommendations, namely recommendations 1.3.1, 1.3.3, 1.3.4 (updated in 2016), 1.4.1, 1.7.4 and 1.8.2.</p> <p><u>Equality issues</u></p> <p>The committee identified race as a potential equality issue, as fibroids are more common in women of African Caribbean descent than other women. However, although prevalence may be higher within this group, there is no difference in treatment options.</p> <p>Fibroids are also more common in women who are overweight. Age was identified as another possible issue, as fibroids become more common with age, and the suitability of treatment may depend on the age of a woman and the proximity to menopause (as fibroids often reduce in size after menopause). Many of the treatments for fibroids (such as hysterectomy) affect fertility, and so a woman's wishes about fertility may influence her choice of treatment for fibroids. None of the currently recommended treatments are suitable for women who are currently trying to conceive. The committee also noted that treatment options which affect regular menstruation may not be favourably considered by some women as in some cultures regular menstrual cycles are considered important. .</p> <p>The Summary of Product Characteristics for ulipristal acetate notes women should avoid conceiving whilst on treatment and that concomitant use of progestogen-only pills, a progestogen-releasing intrauterine device or combined oral contraceptive pills is not recommended and a non-hormonal contraceptive method is recommended during treatment. This will have implications for women who have cultural reasons for not using any form of contraception.</p> <p>Relevant subgroups were also been specified in the review protocol, however, no evidence relating specifically to these subgroups were available in the evidence.</p>

1

2.7.2 Recommendations

- 3 1 Women should be given the following information on potentially unwanted
4 outcomes. [2007, amended 2016]

Treatment	Potential unwanted outcomes experienced by
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	some women (Common: 1 in 100 chance; less common: 1 in 1000 chance; rare: 1 in 10,000 chance; very rare: 1 in 100,000 chance)
Levonorgestrel-releasing intrauterine system [2007]	Common: irregular bleeding that may last for over 6 months; hormone-related problems such as breast tenderness, acne or headaches, which, if present, are generally minor and transient Less common: amenorrhoea Rare: uterine perforation at the time of insertion
Tranexamic acid [2007]	Less common: indigestion; diarrhoea; headaches
Non-steroidal anti-inflammatory drugs [2007]	Common: indigestion; diarrhoea Rare: worsening of asthma in sensitive individuals; peptic ulcers with possible bleeding and peritonitis
Combined oral contraceptives [2007]	Common: mood changes; headaches; nausea; fluid retention; breast tenderness Very rare: deep vein thrombosis; stroke; heart attacks
Oral progestogen (norethisterone) [2007]	Common: weight gain; bloating; breast tenderness; headaches; acne (but all are usually minor and transient) Rare: depression
Injected progestogen [2007]	Common: weight gain; irregular bleeding; amenorrhoea; premenstrual-like syndrome (including bloating, fluid retention, breast tenderness) Less common: small loss of bone mineral density, largely recovered when treatment discontinued
Ulipristal acetate [new 2016]	Very common: endometrial thickening, amenorrhoea Common: vertigo, nausea, abdominal pain, hot flushes, headache, fatigue, ovarian cyst, breast pain and tenderness, pelvic pain, musculoskeletal pain, acne, weight increase Less common: dizziness, dry mouth, constipation, anxiety, urinary incontinence, alopecia, dry skin, hyperhidrosis, back pain, uterine haemorrhage, metrorrhagia, genital discharge, oedema, asthenia, increased blood lipids Rare: epistaxis, dyspepsia, flatulence, ruptured ovarian cyst, breast swelling
Gonadotrophin-releasing hormone analogue [2007]	Common: menopausal-like symptoms (such as hot flushes, increased sweating, vaginal dryness) Less common: osteoporosis, particularly trabecular bone with longer than 6-months' use

Endometrial ablation [2007]	<p>Common: vaginal discharge; increased period pain or cramping (even if no further bleeding); need for additional surgery</p> <p>Less common: infection</p> <p>Rare: perforation (but very rare with second generation techniques)</p>
Uterine artery embolisation [2007]	<p>Common: persistent vaginal discharge; post-embolisation syndrome – pain, nausea, vomiting and fever (not involving hospitalisation)</p> <p>Less common: need for additional surgery; premature ovarian failure particularly in women over 45 years old; haematoma</p> <p>Rare: haemorrhage; non-target embolisation causing tissue necrosis; infection causing septicaemia</p>
Myomectomy [2007]	<p>Less common: adhesions (which may lead to pain and/or impaired fertility); need for additional surgery; recurrence of fibroids; perforation (hysteroscopic route); infection</p> <p>Rare: haemorrhage</p>
Hysterectomy [2007]	<p>Common: infection</p> <p>Less common: intraoperative haemorrhage; damage to other abdominal organs, such as the urinary tract or bowel; urinary dysfunction – frequent passing of urine and incontinence</p> <p>Rare: thrombosis (DVT and clot on the lung)</p> <p>Very rare: death</p> <p>(Complications are more likely when hysterectomy is performed in the presence of fibroids.)</p>
Oophorectomy at time of hysterectomy [2007]	<p>Common: menopausal-like symptoms</p>

- 1 **2 Offer ulipristal acetate 5 mg (up to 4 courses)¹ to women with heavy menstrual**
- 2 **bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level of 102 g**
- 3 **per litre or below. [new 2016]**
- 4 **3 Consider ulipristal acetate 5 mg (up to 4 courses)² for women with heavy menstrual**
- 5 **bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level above 102**
- 6 **g per litre. [new 2016]**

¹ The summary of product characteristics states: 'In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period.'

² The summary of product characteristics states: 'In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period.'

2.81 Research recommendations

2 **What is the efficacy and safety of ulipristal acetate 5 mg for a duration of more than 4**
3 **courses for women with heavy menstrual bleeding and fibroids of 3 cm or more in**
4 **diameter, compared with other uterus-sparing treatments?**

5 **Why this is important**

6 The current evidence suggests that ulipristal acetate 5 mg is an effective treatment for
7 women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter. The
8 evidence covers a period of 4 courses (20 months). Research is needed on the efficacy and
9 safety of ulipristal acetate 5 mg over a period of more than 4 courses, compared with other
10 uterus-sparing treatments.

11 **Table 3: Criteria for selecting high-priority research recommendations**

PICO	<p>Population: Women with heavy menstrual bleeding, fibroids of 3 cm or more in diameter.</p> <p>Intervention: Ulipristal acetate 5 mg, duration > 20 months/4 courses</p> <p>Comparison: other uterus sparing procedures e.g. Uterine artery embolization or myomectomy</p> <p>Outcomes: Efficacy outcomes: Quality of life (assessed using a validated questionnaire such as the USS quality of life scale, SF36, EQ5D) Menstrual blood loss Fibroid volume Uterine volume Bone mineral density Endometrial hyperplasia Preservation of fertility Number of women with regular menstrual cycle Number of women undergoing surgery? Pressure symptoms</p>
Current evidence base	The current evidence suggests that ulipristal acetate 5mg is an effective treatment for women with heavy menstrual bleeding and fibroids of 3cm or more in diameter. The evidence covers a period of 4 courses (20 months). Research is needed on the efficacy and safety of ulipristal acetate 5 mg over a period of more than 4 courses, compared with other uterus sparing treatments.
Study design	RCT in primary & secondary care of ulipristal acetate 5 mg with duration greater than 20 months/4 courses.

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4₁ Glossary and abbreviations

- 2 Please refer to the [NICE glossary](#).
- 3 **Abnormal uterine bleeding:** abnormal uterine bleeding can occur when a woman
4 experiences a change in her menstrual loss, or the degree of loss or vaginal bleeding pattern
5 differs from that experienced by the age-matched general female population.
- 6 **Dysfunctional uterine bleeding:** abnormal vaginal bleeding that occurs during a menstrual
7 cycle that produced no egg (ovulation did not take place). The occurrence of irregular or
8 excessive uterine bleeding in the absence of pregnancy, infection, trauma, new growth or
9 hormone treatment.
- 10 **Endometrium:** the mucous membrane lining the uterus.
- 11 **Endometrial hyperplasia:** abnormal thickening of the lining of the womb, caused by
12 overgrowth of the cells that line the womb.
- 13 **Gonadotrophin releasing hormone (GnRH):** agent that activates the gonadotrophin
14 releasing hormone receptor resulting in increased secretion of follicle-stimulating hormone
15 and luteinising hormone.
- 16 **Leuprorelin acetate:** a synthetic gonadotrophin releasing hormone (GnRH).
- 17 **Mifepristone:** a synthetic steroid and progesterone receptor modulator with an
18 antiprogesterational action as a result of competition with progesterone at the progesterone
19 receptors.
- 20 **Oophorectomy:** surgical removal of one or both ovaries.
- 21 **Ovulation:** the release of a single, mature egg from the ovarian follicle.
- 22 **Pictorial blood loss assessment chart:** a chart for recording the level of menstrual loss
23 based on appearance (PBAC) of sanitary pads. On the basis of the chart results the total
24 amount of menstrual blood loss can be estimated.
- 25 **Progesterone receptor modulators:** an agent that acts on the progesterone receptor.
- 26 **Transvaginal ultrasound (TVS):** transvaginal ultrasound is a method of imaging the genital
27 tract in women. The ultrasound machine sends out high-frequency soundwaves that bounce
28 off body structures to create a picture on a screen. With the transvaginal technique, the
29 ultrasound transducer (a handheld probe) is inserted directly into the vagina. It is therefore
30 closer to pelvic structures than with the conventional transabdominal technique (with the
31 probe on the skin of the abdomen).
- 32 **Ulipristal acetate:** a synthetic progesterone receptor modulator, which partially antagonises
33 progesterone.
- 34 **Uterine fibroids:** smooth-muscle tumours of the uterus, generally benign although
35 occasionally (< 1%) malignant. They vary greatly in size from millimetres to tens of
36 centimetres, and are associated with heavy periods, pressure symptoms and occasionally
37 pain. They are responsive to the female hormones oestrogen and progesterone, generally
38 shrinking to a degree at the menopause.
- 39 **Uterus:** the uterus (womb) is a hollow, pear-shaped organ located in a woman's lower
40 abdomen between the bladder and the rectum. The narrow, lower portion of the uterus is the
41 cervix; the broader, upper part is the corpus. The corpus is made up of two layers of tissue
42 (myometrium and endometrium).

1 Appendices

2 Appendix A: Committee members and 3 NICE teams

A.1 4 Core members

Name	Role
Damien Longson (Chair)	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust
Catherine Briggs (until February 2016)	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies (until February 2016)	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Professor, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Kath Nuttall (until November 2015)	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset
Philippa Williams	Lay Member
Sophie Wilne (Vice Chair)	Paediatric Oncologist, Nottingham Children's Hospital

A.2 5 Topic experts

Name	Role
Sarah Gray	GP Specialist in women's health
Mary Ann Lumsden	Professor of medical education and gynaecology
Alice Pritchard	Lay member
Jan Wake	GP Specialist in sexual and reproductive health

A.3 6 NICE project team

Name	Role
Mark Baker	Clinical Advisor
Steven Barnes	Technical Lead
Christine Carson	Guideline Lead
Jessica Fielding	Public Involvement Advisor
Rupert Franklin	Programme Manager
Bhash Naidoo	Technical Lead (Health Economics)
Louise Shires	Guideline Commissioning Manager
Trudie Willingham	Guideline Co-ordinator

A.4₁ Clinical guidelines update team

Name	Role
Philip Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Anna Zarembo / Ross Maconachie	Health Economist
Sarah Glover	Information Specialist
Kathryn Hopkins / Omnia Abdulrazeg	Technical Analyst
Nick Lowe/Emma Carter	Administrator
Hugh McGuire	Technical Advisor
Susannah Moon	Programme Manager
Ian Pye	Assistant Project Manager
Lorraine Taylor	Associate Director

2

1 **Appendix B: Declarations of interest**

2

3 The standing committee and topic experts interests have been declared and collated and are

4 available [here](#)

1 Appendix C: Review protocol

Review Protocol	
Components	Details
Review question	What is the clinical and cost effectiveness of medical treatment with progesterone receptor modulators ^e for fibroids greater than 3cm in diameter?
Background/objectives	The NICE 2015 surveillance review found evidence on progesterone-receptor modulators (specifically mifepristone and ulipristal acetate) as a potential treatment for fibroids. If progesterone-receptors are effective in the treatment of fibroids, this new evidence may have an impact on current recommendations. The aim of the review is to evaluate the clinical and cost effectiveness of progesterone receptor modulators for the treatment of uterine fibroids greater than 3m in diameter.
Types of study to be included	Randomised controlled trials and systematic reviews of randomised controlled trials* *Systematic reviews of randomised controlled trials will only be included if they meet the quality criteria specified in the NICE manual, and match the review protocol. Other systematic reviews that partially meet the criteria specified in the review protocol will be used for cross checking.
Language	English (original English version or existing full text English translation)
Status	Published papers (full text only)
Population	Women of reproductive age (post puberty and pre-menopausal) with uterine fibroids.
Intervention	Progesterone receptor modulators (for example, Ulipristal acetate, mifepristone)
Comparator	Any other treatment for fibroids (for example, other medical treatment, intrauterine device, uterine artery embolization, myomectomy, hysterectomy). Note that myomectomy and hysterectomy will not be valid comparators for pre surgical treatment (as they as surgical treatments themselves). Placebo, no treatment, usual care Treatment with another progesterone receptor modulator or the same progesterone receptor modulator with a different dose
Outcomes	Quality of life (assessed using a validated questionnaire such as the USS quality of life scale, SF36, EQ5D) The total score will be reported, along with symptom relief and new symptom subscales. Menstrual blood loss Fibroid volume Uterine volume Bone mineral density Endometrial hyperplasia Preservation of fertility Number of women conceiving

^e The term 'progesterone receptor modulator' has been used variably. To avoid doubt, we intend the term to include mifepristone and ulipristal acetate.

Review Protocol	
	<p>Number of women with regular menstrual cycle (surrogate measure)</p> <p>Post hoc amendment: Following completion of the evidence review, the committee requested that data was also presented on the number of participants undergoing surgical/radiological intervention.</p>
Any other information or criteria for inclusion/exclusion	<p>Exclusion criteria: Studies on progesterone receptor modulators with no UK marketing authorisation for any indication. 'Off label' medicines with no marketing authorisation for fibroids, but with a marketing authorisation for another indication will be included.</p> <p>Selection of papers: i) Selection based on titles and abstracts Full double-sifting of titles and abstracts will not be conducted due to the straightforward nature of the review question (intervention question with clearly defined interventions and comparators). ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). Other mechanisms will be in place for quality assurance: The Committee will be sent the list of included and excluded studies prior to the committee meeting, and the Committee will be requested to cross check whether any studies have been excluded inappropriately, and whether there are any relevant studies they have known of which have not been identified by the searches.</p>
Analysis of subgroups or subsets	<p>Fibroids of greater than 3cm in diameter Single vs multiple fibroids Fibroid location (subserosal, submucosal, pedunculated) Pre-surgical vs definitive treatment</p>
Data extraction and quality assessment	<p>Key features of included studies and reported outcomes will be extracted into evidence tables. The quality of evidence for each outcome will be assessed using the approach for intervention questions outlined by the GRADE working group.</p> <p>Reliability of quality assessment: A full double-scoring quality assessment will not be conducted due to the nature of the review question (as mentioned above) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: Internal quality assurance by CGUT technical adviser on the quality assessment that is being conducted. The Committee will be sent the evidence synthesis prior to the committee meeting and the Committee will be requested to comment on the quality assessment, which will serve as another quality assurance function.</p>
Strategy for data synthesis	<p>Data for each outcome from different studies will be synthesised using pairwise meta-analysis where possible. Where synthesis by meta-analysis is not possible, data will be</p>

Review Protocol	
	<p>presented for individual studies.</p> <p>Data from the following time ranges will be pooled: 0-3 months, 3-9 months, over 9 months</p> <p>Studies assessing different progesterone receptor modulators (e.g. ulipristal acetate and mifepristone) will be analysed separately.</p> <p>Studies assessing pre-surgical and longer term treatment will be analysed separately.</p>
Searches	<p>To identify primary literature the following databases will be searched::</p> <p>Medline Medline in Process Embase CDSR CENTRAL DARE HTA PubMed</p> <p>To identify the Health Economic literature the following databases will be searched:</p> <p>Medline Medline in Process Embase NHS EED – archive HTA</p> <p>No supplementary search techniques are planned</p> <p>The following limits will be applied:</p> <p>RCT and Systematic Review study filters will be applied to identify the primary literature</p> <p>For the health economic searches Health Economic and Quality of Life filters will be applied</p> <p>Searches will be limited to English language papers</p> <p>Searches will be limited to human studies</p>

1 Appendix D: Search strategy

2 Sources searched to identify the clinical evidence:

3 **Table 4: Clinical search summary**

Databases	Date searched	Version/files	No. retrieved	RefMan data
MEDLINE (Ovid)	17/09/2015	1946 to September Week 2 2015	339	1-333
MEDLINE In-Process (Ovid)	17/09/2015	September 16, 2015	24	334-354
EMBASE (Ovid)	17/09/2015	1974 to 2015 Week 37	386	355-636
Cochrane Central Register of Controlled Trials (CENTRAL)	22/09/2015	Issue 8 of 12, August 2015	141	646-732
Cochrane Database of Systematic Reviews (CDSR)	22/09/2015	Issue 9 of 12, September 2015	7	637-642
Database of Abstracts of Reviews of Effectiveness (DARE)	22/09/2015	Issue 2 of 4, April 2015	3	643-645
Health Technology Assessment (HTA)	22/09/2015	Issue 3 of 4, July 2015	4	733-735
PubMed	22/09/2015	-	21	736-754

4 The MEDLINE search strategy is presented below. This was translated for use in all of the
5 other databases listed. The aim of the search was to identify evidence for the clinical
6 question being asked.

7 The Pubmed translation consisted of an abbreviated strategy run at the end of the process
8 designed to capture references that had not yet appeared in the Medline in Process
9 database. Randomised Controlled Trial and Systematic Review filters were used to identify
10 the study designs specified in the Review Protocol.

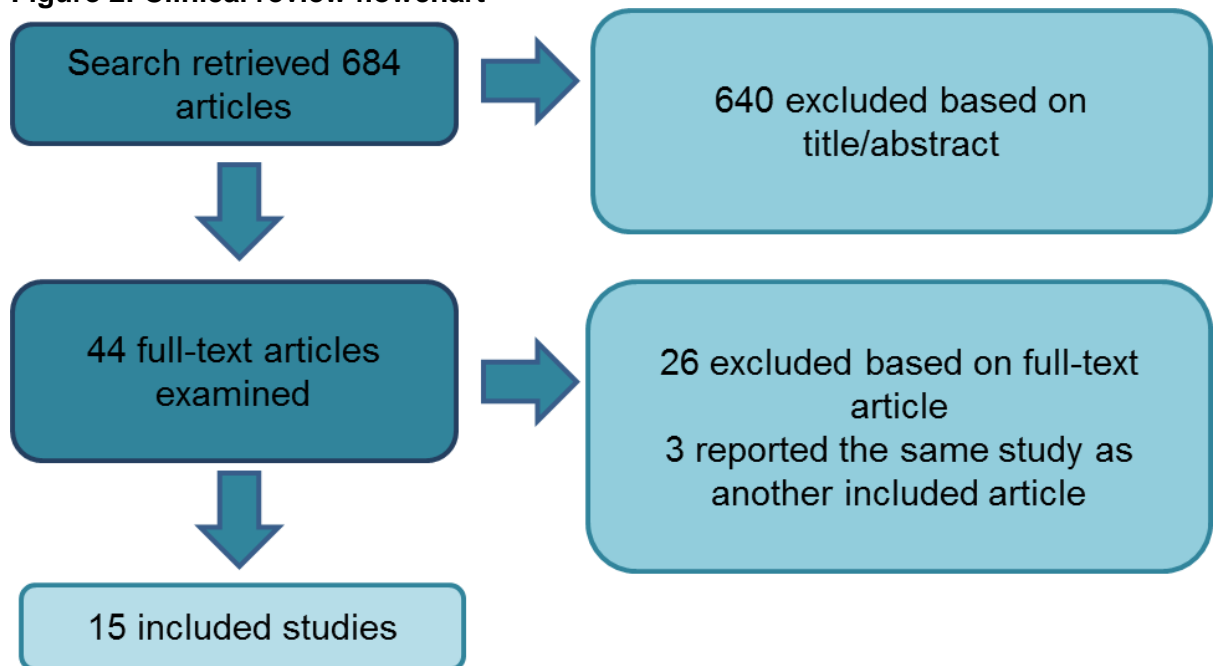
11 **Table 5: Clinical search terms (Medline and Medline in process)**

Line number/Search term/Number retrieved	
1	exp Leiomyoma/ (17894)
2	Uterine Neoplasms/ (35946)
3	(leiomyoma* or leimyoma*).tw. (10612)
4	leyomyoma*.tw. (5)
5	(angioleiomyoma* or angiomyoma* or elastomyofibroma* or h?emangioleiomyoma* or h?emangiomyoma* or myofibroma* or myofibromatosis or leiomyoblastoma*).tw. (1304)
6	fibroid*.tw. (4030)
7	fibromyoma*.tw. (624)
8	fibroma*.tw. (9478)
9	myoma*.tw. (4537)
10	(smooth adj4 muscle adj4 (tumour* or tumor*).tw. (1962)
11	Menorrhagia/ (3725)
12	(menorrhag* or hypermenorrh*).tw. (2846)
13	((menstru* or period*) adj4 (bleed* or blood* or flow* or loss)).tw. (19385)
14	(dysfunctional adj4 uterine adj4 bleed*).tw. (780)
15	(dysfunctional adj4 uterine adj4 blood*).tw. (5)
16	or/1-15 (80836)
17	Receptors, Progesterone/ (16562)

Line number/Search term/Number retrieved	
18	((progestin* or progesterone*) adj4 receptor*).tw. (18890)
19	(Ulipristal* or uliprisnil*).tw. (133)
20	(esmya or ella or ellaone or ella one).tw. (196)
21	Mifepristone/ (5476)
22	(mifepriston* or mifegyne or korlym or mifeprex).tw. (2746)
23	Norpregnadienes/ (493)
24	(Norpregnadiene* or norpregnane* or norpregnatriene* or norpregnene* or pregnadiene* or pregnadienediol* or pregnane* or pregnatriene* or pregnenedione* or pregnene*).tw. (4744)
25	or/17-24 (33951)
26	16 and 25 (1305)
27	animals/ not humans/ (4017726)
28	26 not 27 (1244)
29	limit 28 to english language (1029)
30	Randomized Controlled Trial.pt. (410388)
31	Controlled Clinical Trial.pt. (91596)
32	Clinical Trial.pt. (504650)
33	exp Clinical Trials as Topic/ (300501)
34	Placebos/ (33985)
35	Random Allocation/ (86086)
36	Double-Blind Method/ (134743)
37	Single-Blind Method/ (21286)
38	Cross-Over Studies/ (37117)
39	((random\$ or control\$ or clinical\$) adj3 (trial\$ or stud\$)).tw. (798811)
40	(random\$ adj3 allocat\$).tw. (22488)
41	placebo\$.tw. (162343)
42	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw. (131780)
43	(crossover\$ or (cross adj over\$)).tw. (59849)
44	or/30-43 (1479476)
45	Meta-Analysis.pt. (59728)
46	Meta-Analysis as Topic/ (14883)
47	Review.pt. (2005427)
48	exp Review Literature as Topic/ (8381)
49	(metaanaly\$ or metanaly\$ or (meta adj3 analy\$)).tw. (70874)
50	(review\$ or overview\$).ti. (290137)
51	(systematic\$ adj5 (review\$ or overview\$)).tw. (65645)
52	((quantitative\$ or qualitative\$) adj5 (review\$ or overview\$)).tw. (4883)
53	((studies or trial\$) adj2 (review\$ or overview\$)).tw. (27030)
54	(integrat\$ adj3 (research or review\$ or literature)).tw. (6056)
55	(pool\$ adj2 (analy\$ or data)).tw. (15884)
56	(handsearch\$ or (hand adj3 search\$)).tw. (5738)
57	(manual\$ adj3 search\$).tw. (3437)
58	or/45-57 (2177457)
59	44 or 58 (3398479)
60	29 and 59 (339)

1 Appendix E: Review flowchart

Figure 2: Clinical review flowchart



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1 Appendix F: Excluded studies

Study	Reason for Exclusion
Bouchard,P., Chabbert-Buffet,N., Fauser,B.C., 20111215, Selective progesterone receptor modulators in reproductive medicine: pharmacology, clinical efficacy and safety, Fertility & Sterility, 96, 1175-1189, 2011	Incorrect study type: non-systematic review (no explicit inclusion/exclusion criteria)
Carbonell Esteve,J.L., Quiroz Ramirez,G.M., Borge,A., Castellon Zapata,L.E., Aragon,W.C., Tomasi,G., 5 mg versus 10 mg mifepristone daily in the treatment of leiomyoma: A randomised clinical trial. [Spanish], Progresos de Obstetricia y Ginecologia, 53, 51-58, 2010	Article not in English.
Carbonell,J.L., Acosta,R., Perez,Y., Yero,M.C., Seigler,I., Heredia,B., Evolution of uterine leiomyoma after treatment with mifepristone. Randomized clinical trial. [Spanish], Progresos de Obstetricia y Ginecologia, 53, 231-236, 2010	Article not in English.
Chwalisz,K., Parker,R.L., Williamson,S., Lois,Larsen, McCrary,K., Elger,W., Treatment of uterine leiomyomas with the novel selective progesterone receptor modulator (SPRM), Journal of the Society for Gynecologic Investigation, 10, 301A-, 2003	Abstract only: no full text article available
Donnez,J., Tomaszewski,J., Vazquez,F., Bouchard,P., Lemieszczuk,B., Baro,F., Nouri,K., Selvaggi,L., Sadowski,K., Bestel,E., Terrill,P., Osterloh,I., Loumaye,E., Ulipristal acetate versus leuprolide acetate for uterine fibroids, Obstetrical and Gynecological Survey.68 (2) (pp 99-100), 2013.Date of Publication: February 2013., 99-100, 2013	Incorrect study type: commentary.
Eisinger,S.H., Bonfiglio,T., Fiscella,K., Meldrum,S., Guzick,D.S., Twelve month safety and efficacy of low dose mifepristone for uterine fibroids, Advances in Uterine Leiomyoma Research: 2nd NIH International Congress, -, 2005	Abstract only: no full text article available.
Eisinger,S.H., Fiscella,K., Meldrum,S., Feng,C., Fisher,S., Guzick,D.S., Effect of mifepristone on quality of life for women with symptomatic fibroids, Fertility and sterility, 86, S41-S42, 2006	Abstract only: no full text article available.
Engman,M., Granberg,S., Williams,A.R.W., Meng,C.X., Lalitkumar,P.G.L., Gemzell-Danielsson,K., Mifepristone for treatment of uterine leiomyoma: A prospective randomized placebo controlled trial, Obstetrical and Gynecological Survey.65 (2) (pp 99-101), 2010.Date of Publication: February 2010., 99-101, 2010	Incorrect study type: commentary.
Fauser,B., Oliver,J., Loumaye,E., Fibroid volume reduction induced by ulipristal acetate (UPA) following fibroid characteristics at baseline post-HOC analyses of pearl i study, Human reproduction (Oxford, England), 28, i116-, 2013	Abstract only: no full text article available.
Feng,C., Meldrum,S., Fiscella,K., 20100716, Improved quality of life is partly explained by fewer symptoms after treatment of fibroids with mifepristone, International Journal of Gynaecology & Obstetrics, 109, 121-124, 2010	Incorrect study type: Synthesis of previous trial and non-comparative study
Fiscella,K., Eisinger,S., 20081113, CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial, Obstetrics & Gynecology, 112, 707-708, 2008	Incorrect study type: commentary.
Galliano,D., 20150423, Ulipristal acetate in uterine fibroids. [Review], Fertility & Sterility, 103, 359-360, 2015	Incorrect study type: Commentary.
Green,L.J., Levy,G., Wesley,R., Nieman,L., Armstrong,A., Efficacyof ulipristal acetate forthe treatment of symptomatic uterine leiomyomas in African Americans, Fertility and sterility, 98, S96-, 2012	Abstract only: no full text article available.
Kulshrestha,V., Kriplani,A., Agarwal,N., Garg,P., Kachhawa,G., Role	Abstract only: no full text

Study	Reason for Exclusion
of mifepristone (RU 486) in management of uterine leiomyoma, Journal of obstetrics and gynaecology, 31, 39-40, 2011	article available.
Murphy,A.A., RU 486 in the treatment of leiomyomata uteri, Infertility and Reproductive Medicine Clinics of North America.7 (1) (pp 57-68), 1996.Date of Publication: 1996., 57-68, 1996	Incorrect study type: narrative review
Orozco,L.J., Clarke,J., Tristan,M., Spies,J.B., Stone,P., Mifepristone for uterine fibroids, Cochrane Database of Systematic Reviews, -, 2009	Systematic review protocol only: no results reported
Pohl,O., Osterloh,I., Gotteland,J.P., 20140227, Ulipristal acetate - safety and pharmacokinetics following multiple doses of 10-50 mg per day, Journal of Clinical Pharmacy & Therapeutics, 38, 314-320, 2013	Incorrect population: healthy volunteers.
Shen,Q., Hua,Y., Jiang,W., Zhang,W., Chen,M., Zhu,X., 20140129, Effects of mifepristone on uterine leiomyoma in premenopausal women: a meta-analysis, Fertility & Sterility, 100, 1722-1726, 2013	Systematic review meeting part of the review protocol only: used for cross checking
Steinauer,J., Pritts,E.A., Jackson,R., Jacoby,A.F., 20040702, Systematic review of mifepristone for the treatment of uterine leiomyomata. [Review] [29 refs], Obstetrics & Gynecology, 103, 1331-1336, 2004	Systematic review partly matching review protocol. Used for cross checking.
Stovall,D.W., Mikdachi,H.E., Treatment of symptomatic uterine leiomyomas with selective progesterone receptor modulators, Expert Review of Obstetrics and Gynecology.6 (6) (pp 579-582), 2011.Date of Publication: November 2011., 579-582, 2011	Incorrect study type: Narrative review
Tafi,E., Scala,C., Maggiore,U.L.R., Bizzarri,N., Candiani,M., Venturini,P.L., Ferrero,S., Drug safety evaluation of ulipristal acetate in the treatment of uterine fibroids, Expert Opinion on Drug Safety.14 (6) (pp 965-977), 2015.Date of Publication: 01 Jun 2015., 965-977, 2015	Incorrect study type: non-systematic review.
Tristan,M., Orozco,L.J., Steed,A., Ramirez-Morera,A., Stone,P., 20120926, Mifepristone for uterine fibroids. [Review], Cochrane Database of Systematic Reviews, 8, CD007687-, 2012	Systematic review parting matching review protocol: used for cross checking.
Tropeano,G., Amoroso,S., Scambia,G., 20080527, Non-surgical management of uterine fibroids. [Review] [184 refs], Human Reproduction Update, 14, 259-274, 2008	Exclude: Systematic review of non-randomised controlled trials.
Tsoi,B., Blackhouse,G., Ferrazzi,S., Reade,C.J., Chen,I., Goeree,R., 20150506, Incorporating ulipristal acetate in the care of symptomatic uterine fibroids: a Canadian cost-utility analysis of pharmacotherapy management, Clinicoeconomics & Outcomes Research, 7, 213-225, 2015	Incorrect study type: Economic analysis
Verguts,J., Orye,G., Marquette,S., Symptom relief of leiomyomatosis peritonealis disseminata with ulipristal acetate, Gynecol Surg., 11, 57-58, 2014	Incorrect study type: case study.
Zeng,C., Gu,M., Huang,H., [A clinical control study on the treatment of uterine leiomyoma with gonadotrophin releasing hormone agonist or mifepristone], Zhonghua fu chan ke za zhi, 33, 490-492, 1998	Article not in English.

1

2

1 Appendix G: Evidence tables

2 Table 6: Bagaria 2009

Bibliographic reference	Bagaria M, Suneja A, Vaid NB et al. (2009) Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. Australian & New Zealand Journal of Obstetrics & Gynaecology 49: 77-83													
Study type	Randomised controlled trial													
Aim	To evaluate the effect of low-dose mifepristone on fibroid-related symptoms in women with symptomatic fibroids													
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Premenopausal women. - Symptomatic uterine fibroids. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Pregnancy or lactation - Suspicion or documented evidence of ovarian, cervical or uterine malignancy - Hormonal treatment in the last 3 months - Histopathological evidence of endometrial hyperplasia - Presence of liver, respiratory, renal, heart or pelvic inflammatory disease, or any other adenexal pathology - Patient necessitating earlier surgical intervention for fibroids. <p>Baseline characteristics (of randomised population)</p> <table border="1"> <thead> <tr> <th></th><th>Mifepristone 10mg/d</th><th>Placebo</th></tr> </thead> <tbody> <tr> <td>Age (mean,sd)</td><td>40.3 (6.8)</td><td>41.1 (9.3)</td></tr> <tr> <td>Race</td><td>not reported</td><td>not reported</td></tr> <tr> <td>Fibroid type</td><td>not reported</td><td>not reported</td></tr> </tbody> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Mifepristone 10mg/d	Placebo	Age (mean,sd)	40.3 (6.8)	41.1 (9.3)	Race	not reported	not reported	Fibroid type	not reported	not reported
	Mifepristone 10mg/d	Placebo												
Age (mean,sd)	40.3 (6.8)	41.1 (9.3)												
Race	not reported	not reported												
Fibroid type	not reported	not reported												
Number of Patients	<table border="1"> <thead> <tr> <th></th><th>Mifepristone 10mg/d</th><th>Placebo</th></tr> </thead> <tbody> <tr> <td>N (Randomised)</td><td>20</td><td>20</td></tr> </tbody> </table>			Mifepristone 10mg/d	Placebo	N (Randomised)	20	20						
	Mifepristone 10mg/d	Placebo												
N (Randomised)	20	20												

Bibliographic reference	Bagaria M, Suneja A, Vaid NB et al. (2009) Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. Australian & New Zealand Journal of Obstetrics & Gynaecology 49: 77-83		
	N (Analysis)	19	16
	Drop outs	1 Lost to follow up (1)	4 Lost to follow up (2) Discontinued treatment (2)
Intervention	Mifepristone 10mg/d		
Comparison	Placebo		
Methods	Participants were randomised to receive mifepristone (10mg/d) or placebo for 3 months. Treatment started between days 1 to 3 of the menstrual cycle.		
Length of follow up	3 months treatment duration		
Location	India, secondary care setting		
Outcomes measures and effect size	Fibroid volume – total volume		
		Mifepristone 10mg/d	Placebo
	Baseline	mean=137.3 sd=217.8 mean(log transformed)=1.6 sd(log values)=0.7 n=19	mean=117.7 sd=243.4 mean(log transformed)=1.3 sd(log values)=0.7 n=19
	End (3 months treatment)	mean=95.8 sd=181 mean(log transformed)=1.3 sd(log values)=0.7 n=19	mean=118.3 sd=243.4 mean(log transformed)=1.6 sd(log values)=0.7 n=19
	Fibroid volume – largest fibroid volume		
	Mifepristone 10mg/d	Placebo	
Baseline	mean=140.4 sd=216.5 mean(log transformed)=1.6	mean=118.1 sd=243.4 mean(log	

Bibliographic reference	Bagaria M, Suneja A, Vaid NB et al. (2009) Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. Australian & New Zealand Journal of Obstetrics & Gynaecology 49: 77-83		
		sd(log values)=0.6 n=19	transformed)=1.3 sd(log values)=0.7 n=19
	End (3 months treatment)	mean=97.5 sd=180.3 mean(log transformed)=1.4 sd(log values)=0.7 n=19	mean=118.7 sd=243.4 mean(log transformed)=1.4 sd(log values)=0.7 n=19
	Uterine volume – total volume		
		Mifepristone 10mg/d	Placebo
	Baseline	mean=256.2 sd=235.6 mean(log transformed)=2.2 sd(log values)=0.3 n=19	mean=281.6 sd=417.5 mean(log transformed)=2.1 sd(log values)=0.4 n=19
Source of funding	Not reported		
Comments	Randomisation: Randomisation was via computer generated random number tables. Allocation concealment: Medication was placed in identical containers according to the random allocation, by a		

Bibliographic reference	Bagaria M, Suneja A, Vaid NB et al. (2009) Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. Australian & New Zealand Journal of Obstetrics & Gynaecology 49: 77-83
	third party and the containers were labelled 1-40. Participants were given the containers sequentially on enrolment. Blinding: Participants and investigators were blind to study allocation. Other:

1 **Table 7: Carbonell 2008**

Bibliographic reference	Carbonell Esteve JL, Acosta R, Heredia B et al. (2008) Mifepristone for the treatment of uterine leiomyomas: a randomized controlled trial. Obstetrics & Gynecology 112: 1029-36
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and safety of 5 mg and 10 mg mifepristone for the treatment of uterine fibroids.
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - - Women of reproductive age - - Symptomatic uterine fibroids - - Agree to use non-hormonal contraception <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Pregnancy or the desire to become pregnant. - Breastfeeding - hormonal contraception or any hormonal therapy in the last 3 months - pelvic inflammatory disease, - adnexal tumours, - abnormal or unexplained uterine bleeding - diagnosis or suspicion of malignant neoplasm - signs or symptoms of mental illness, - adrenal disease - sickle-cell disease - hepatic disease - renal disease - Bleeding disorders - antiprogesterone contraindications

Bibliographic reference	Carbonell Esteve JL, Acosta R, Heredia B et al. (2008) Mifepristone for the treatment of uterine leiomyomas: a randomized controlled trial. Obstetrics & Gynecology 112: 1029-36													
	Baseline characteristics (of randomised population) <table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> <tr> <td>Age (mean,sd)</td><td>42.8 (5.8)</td><td>39.5 (6.6)</td></tr> <tr> <td>Race</td><td>White (19) Black (24) Afro-Cuban (7)</td><td>White (10) Black (33) Afro-Cuban (7)</td></tr> <tr> <td>Fibroid type</td><td>not reported</td><td>not reported</td></tr> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Mifepristone 5mg/d	Mifepristone 10mg/d	Age (mean,sd)	42.8 (5.8)	39.5 (6.6)	Race	White (19) Black (24) Afro-Cuban (7)	White (10) Black (33) Afro-Cuban (7)	Fibroid type	not reported	not reported
	Mifepristone 5mg/d	Mifepristone 10mg/d												
Age (mean,sd)	42.8 (5.8)	39.5 (6.6)												
Race	White (19) Black (24) Afro-Cuban (7)	White (10) Black (33) Afro-Cuban (7)												
Fibroid type	not reported	not reported												
Number of Patients	<table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> <tr> <td>N (Randomised)</td><td>50</td><td>50</td></tr> <tr> <td>Drop outs</td><td>0</td><td>1 Expelled fibroid(1)</td></tr> </table>			Mifepristone 5mg/d	Mifepristone 10mg/d	N (Randomised)	50	50	Drop outs	0	1 Expelled fibroid(1)			
	Mifepristone 5mg/d	Mifepristone 10mg/d												
N (Randomised)	50	50												
Drop outs	0	1 Expelled fibroid(1)												
Intervention	Mifepristone 5mg/d													
Comparison	Mifepristone 10mg/d													
Methods	Participants were randomised to receive either 5 or 10mg of mifepristone for 3 months.													
Length of follow up	3 month treatment period													
Location	Cuba. Secondary care setting.													
Outcomes measures and effect size	Fibroid volume evaluated by ultrasound <table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> <tr> <td>Baseline</td><td>mean=172cm³ sd=161 n=50</td><td>mean=187cm³ sd=184 n=50</td></tr> <tr> <td>End of treatment (3 months)</td><td>mean=77cm³ sd=125 n=50</td><td>mean=103cm³ sd=124 n=49</td></tr> </table>			Mifepristone 5mg/d	Mifepristone 10mg/d	Baseline	mean=172cm ³ sd=161 n=50	mean=187cm ³ sd=184 n=50	End of treatment (3 months)	mean=77cm ³ sd=125 n=50	mean=103cm ³ sd=124 n=49			
	Mifepristone 5mg/d	Mifepristone 10mg/d												
Baseline	mean=172cm ³ sd=161 n=50	mean=187cm ³ sd=184 n=50												
End of treatment (3 months)	mean=77cm ³ sd=125 n=50	mean=103cm ³ sd=124 n=49												

Bibliographic reference	Carbonell Esteve JL, Acosta R, Heredia B et al. (2008) Mifepristone for the treatment of uterine leiomyomas: a randomized controlled trial. <i>Obstetrics & Gynecology</i> 112: 1029-36	
	Uterine volume evaluated by ultrasound	
	Uterine hyperplasia (biopsy)	
reported but not extracted: pelvic pain, pelvic pressure, urinary symptoms, lower back pain, rectal pain, dyspareunia, hypermenorrhoea, metrorrhagia, amenorrhea, hot flushes		
Source of funding	Not reported – authors state that there were no conflicts of interest	
Comments	<p>Randomisation: Randomisation was via a computer generated list.</p> <p>Allocation concealment: Sequentially numbered sealed envelopes contained the treatment allocation. Once the participant was enrolled in the trial the envelope was opened by the study doctor and the participant was assigned to the allocation within the envelope.</p> <p>Blinding: Researchers and patients were blind to treatment allocation.</p> <p>Other:</p>	

1 Table 8: Carbonell 2012

Bibliographic reference	Carbonell Esteve JL, Riveron AM, Cano M et al. (2012) Mifepristone 2.5 mg versus 5 mg daily in the treatment of leiomyoma before surgery. <i>International Journal of Women's Health</i> 4: 75-84
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and safety of 2.5 mg and 5 mg mifepristone for the treatment of uterine fibroids before surgery.
Patient characteristics	Inclusion criteria:

Bibliographic reference	Carbonell Esteve JL, Riveron AM, Cano M et al. (2012) Mifepristone 2.5 mg versus 5 mg daily in the treatment of leiomyoma before surgery. International Journal of Women's Health 4: 75-84		
	<ul style="list-style-type: none">- Women of childbearing age- Symptomatic uterine fibroids requiring treatment to improve general condition before hysterectomy or myomectomy- Clinical indications for myomectomy or hysterectomy		
	Exclusion criteria: <ul style="list-style-type: none">- Pregnancy or the desire to become pregnant.- Breastfeeding- hormonal contraception or any hormonal therapy in the last 3 months- signs or symptoms of pelvic inflammation,- adnexal tumours,- suspicion or diagnosis of cervical–uterine or ovarian cancer,- signs or symptoms of mental illness,- unexplained genital bleeding,- anaemia due to sickle-cell disease,- suffering from a serious illness,- antiprogesterone contraindications		
	Baseline characteristics (of randomised population)		
		Mifepristone 2.5mg/d	Mifepristone 5mg/d
	Age (mean,sd)	42.3 (5.8)	42.0 (6.7)
Race	White (23) Black (18) Afro-Cuban (30)	White (18) Black (18) Afro-Cuban (39)	
Fibroid type	not reported	not reported	
See outcome measures for baseline measures of reported outcomes			
Number of Patients			
	Mifepristone 2.5mg/d	Mifepristone 5mg/d	
N (Randomised)	71	75	

Bibliographic reference	Carbonell Esteve JL, Riveron AM, Cano M et al. (2012) Mifepristone 2.5 mg versus 5 mg daily in the treatment of leiomyoma before surgery. International Journal of Women's Health 4: 75-84			
	Drop outs	12 Lost to follow up (4) Underwent surgery for fibroid necrobiosis before end of treatment (1) Abandoned trial (3)	4 Underwent surgery for fibroid necrobiosis before end of treatment (1) Fibroid expulsion (1) Elevated transaminases (1) Abandoned trial (1)	
Intervention	Mifepristone 2.5mg/d			
Comparison	Mifepristone 5mg/d			
Methods	Participants were scheduled for either a myomectomy or hysterectomy. They were randomised to receive either 2.5 or 5mg of mifepristone in the 3 months before surgery.			
Length of follow up	3 month treatment period			
Location	Cuba and Nicaragua (multi-centre study). Secondary care setting.			
Outcomes measures and effect size	Fibroid volume evaluated by ultrasound			
		Mifepristone 2.5mg/d	Mifepristone 5mg/d	
	Baseline	mean=119cm ³ sd=107 n=48	mean=140cm ³ sd=144 n=60	
	End of treatment (3 months)	mean=73cm ³ sd=82 n=48	mean=64cm ³ sd=76 n=60	
	Uterine volume evaluated by ultrasound			
		Mifepristone 2.5mg/d	Mifepristone 5mg/d	
	Baseline	mean=384cm ³ sd=246 n=48	mean=538cm ³ sd=390 n=60	
	End of treatment (3 months)	mean=347cm ³ sd=267 n=48	mean=407cm ³ sd=357 n=60	

Bibliographic reference	Carbonell Esteve JL, Riveron AM, Cano M et al. (2012) Mifepristone 2.5 mg versus 5 mg daily in the treatment of leiomyoma before surgery. International Journal of Women's Health 4: 75-84																			
	<p>Endometrial hyperplasia – data not used in analysis (no denominators available) *denominator not reported, and reviewer unable to infer</p> <table> <tr> <th></th><th>Mifepristone 2.5mg/d</th><th>Mifepristone 5mg/d</th></tr> <tr> <td>Baseline</td><td>0/?*</td><td>0/?*</td></tr> <tr> <td>End of treatment (3 months)</td><td>0/?*</td><td>0/?*</td></tr> </table> <p>Endometrial thickness (surrogate for endometrial hyperplasia)</p> <table> <tr> <th></th><th>Mifepristone 2.5mg/d</th><th>Mifepristone 5mg/d</th></tr> <tr> <td>Baseline</td><td>mean=6.8mm sd=2.0 n=48</td><td>mean=7.3mm sd=2.7 n=60</td></tr> <tr> <td>End of treatment (3 months)</td><td>mean=9.4mm sd=3.7 n=48</td><td>mean=10.3mm sd=4.5 n=60</td></tr> </table> <p>reported but not extracted: Intermediate time points (1 month, 2 months of treatment) also reported, haemoglobin, pelvic pain, hypermenorrhoea, pelvic pressure, urinary alterations, rectal or lumbar pain, metrorrhagia, side effects not specified in review protocol, change in liver transaminase levels, length of surgery, intraoperative bleeding, post-surgery hospital stay, haemoglobin after surgery</p>			Mifepristone 2.5mg/d	Mifepristone 5mg/d	Baseline	0/?*	0/?*	End of treatment (3 months)	0/?*	0/?*		Mifepristone 2.5mg/d	Mifepristone 5mg/d	Baseline	mean=6.8mm sd=2.0 n=48	mean=7.3mm sd=2.7 n=60	End of treatment (3 months)	mean=9.4mm sd=3.7 n=48	mean=10.3mm sd=4.5 n=60
	Mifepristone 2.5mg/d	Mifepristone 5mg/d																		
Baseline	0/?*	0/?*																		
End of treatment (3 months)	0/?*	0/?*																		
	Mifepristone 2.5mg/d	Mifepristone 5mg/d																		
Baseline	mean=6.8mm sd=2.0 n=48	mean=7.3mm sd=2.7 n=60																		
End of treatment (3 months)	mean=9.4mm sd=3.7 n=48	mean=10.3mm sd=4.5 n=60																		
Source of funding	Not reported (authors state that there were no conflicts of interest to declare)																			
Comments	<p>Randomisation: Randomisation was via a computer generated list.</p> <p>Allocation concealment: Staff not involved in the trial produced opaque sequentially numbered sealed envelopes containing the treatment allocation. Once the participant was enrolled in the trial the envelope was opened and the participant was assigned to the allocation within the envelope.</p> <p>Blinding: No details of blinding: presume unblinded due to method of treatment allocation.</p> <p>Other: Reports that data was incorporated up to the point of dropout, but this seems to be inconsistent with numbers reported in tables – appears that only cases that did not dropout were included. Uterine volume appears larger at baseline in the 5mg group. Significantly higher dropout rate in 2.5mg group.</p>																			

1 **Table 9: Carbonell 2013a**

Bibliographic reference	Carbonell JL, Acosta R, Perez Y et al. (2013) Treatment of Uterine Myoma with 2.5 or 5mg Mifepristone Daily during 3 Months with 9 Months Posttreatment Followup: Randomized Clinical Trial. ISRN Obstetrics & Gynecology 2013: 649030													
Study type	Randomised controlled trial													
Aim	To evaluate the efficacy and safety of 2.5 mg and 5 mg mifepristone for the treatment of uterine fibroids during after 3 months of treatment and 9 months of subsequent follow up.													
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Women of childbearing age 18+ - Symptomatic uterine fibroids requiring treatment to improve general condition before hysterectomy or myomectomy - Clinical indications for myomectomy or hysterectomy <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Pregnancy or the desire to become pregnant. - Breastfeeding - hormonal contraception or any hormonal therapy in the last 3 months - signs or symptoms of pelvic inflammation, - adnexal tumours, - suspicion or diagnosis of cervical–uterine or ovarian cancer, - signs or symptoms of mental illness, - unexplained genital bleeding, - anaemia due to sickle-cell disease, - suffering from a serious illness, - antiprogesterone contraindications <p>Baseline characteristics (of randomised population)</p> <table> <tr> <th></th><th>Mifepristone 2.5mg/d</th><th>Mifepristone 5mg/d</th></tr> <tr> <td>Age (mean,sd)</td><td>39.6 (6.0)</td><td>39.0 (5.9)</td></tr> <tr> <td>Race</td><td>White (32) Black (36) Afro-Cuban (42)</td><td>White (27) Black (49) Afro-Cuban (34)</td></tr> <tr> <td>Fibroid</td><td>Not reported</td><td>Not reported</td></tr> </table>			Mifepristone 2.5mg/d	Mifepristone 5mg/d	Age (mean,sd)	39.6 (6.0)	39.0 (5.9)	Race	White (32) Black (36) Afro-Cuban (42)	White (27) Black (49) Afro-Cuban (34)	Fibroid	Not reported	Not reported
	Mifepristone 2.5mg/d	Mifepristone 5mg/d												
Age (mean,sd)	39.6 (6.0)	39.0 (5.9)												
Race	White (32) Black (36) Afro-Cuban (42)	White (27) Black (49) Afro-Cuban (34)												
Fibroid	Not reported	Not reported												

Bibliographic reference	Carbonell JL, Acosta R, Perez Y et al. (2013) Treatment of Uterine Myoma with 2.5 or 5mg Mifepristone Daily during 3 Months with 9 Months Posttreatment Followup: Randomized Clinical Trial. ISRN Obstetrics & Gynecology 2013: 649030		
	type		
	See outcome measures for baseline measures of reported outcomes		
Number of Patients			
		Mifepristone 2.5mg/d	Mifepristone 5mg/d
	N (Randomised)	110	110
	Drop outs	3 month treatment period (8) 0-3 months follow up (4) 3-6 months follow up (5) 6-9 months follow up (3)	3 month treatment period (4) 0-3 months follow up (2) 3-6 months follow up (1) 6-9 months follow up (3)
Intervention	Mifepristone 2.5mg/d (half tablet once per day)		
Comparison	Mifepristone 5mg/d (whole tablet once per day)		
Methods	Participants were randomised to receive 2.5mg/d or 5mg/d of mifepristone for 3 months. They were then followed up for 9 months after treatment, with follow up visits at 3, 6 and 9 months after treatment.		
Length of follow up	3 month treatment period, 9 months follow up		
Location	Cuba. Secondary care setting.		
Outcomes measures and effect size	Fibroid volume evaluated by ultrasound		
		Mifepristone 2.5mg/d	Mifepristone 5mg/d
	Baseline	mean=136cc sd=129 n=110	mean=112cc sd=118 n=110
	End of treatment (3 months)	mean=98 sd=107 n=102	mean=60 sd=67 n=106
	3 months follow up	mean=115 sd=144 n=98	mean=80 sd=109 n=104
	6 months follow up	mean=112 sd=141	mean=81 sd=110

Bibliographic reference	Carbonell JL, Acosta R, Perez Y et al. (2013) Treatment of Uterine Myoma with 2.5 or 5mg Mifepristone Daily during 3 Months with 9 Months Posttreatment Followup: Randomized Clinical Trial. ISRN Obstetrics & Gynecology 2013: 649030		
	9 months follow up	n=93	n=103
		mean=129	mean=99
		sd=157	sd=91
		n=90	n=100
	Uterine volume evaluated by ultrasound		
		Mifepristone 2.5mg/d	Mifepristone 5mg/d
	Baseline	mean=455cc sd=314 n=110	mean=426cc sd=305 n=110
	End of treatment (3 months)	mean=372cc sd=272 n=102	mean=332cc sd=243 n=106
	3 months follow up	mean=418 sd=266 n=98	mean=379 sd=320 n=104
	6 months follow up	mean=437 sd=274 n=93	mean=478 sd=255 n=103
	9 months follow up	mean=495 sd=321 n=90	mean=489 sd=265 n=100
	Endometrial hyperplasia (biopsy)		
		Mifepristone 2.5mg/d	Mifepristone 5mg/d
	End of treatment (3 months)	0/66	0/68
	*not all women underwent biopsy, and some biopsies were unsuitable for diagnosis		
	Endometrial thickness (surrogate for endometrial hyperplasia)		

Bibliographic reference	Carbonell JL, Acosta R, Perez Y et al. (2013) Treatment of Uterine Myoma with 2.5 or 5mg Mifepristone Daily during 3 Months with 9 Months Posttreatment Followup: Randomized Clinical Trial. ISRN Obstetrics & Gynecology 2013: 649030		
		Mifepristone 2.5mg/d	Mifepristone 5mg/d
	Baseline	mean=6.8mm sd=1.9 n=110	mean=6.8mm sd=1.9 n=110
	End of treatment (3 months)	mean=8.9mm sd=3.7 n=102	mean=9.0mm sd=3.7 n=106
	3 months follow up	mean=7.7mm sd=2.3 n=98	mean=7.8mm sd=2.3 n=104
	6 months follow up	mean=7.7mm sd=2.4 n=93	mean=7.9mm sd=2.8 n=103
	9 months follow up	mean=7.5mm sd=1.9 n=90	mean=7.5mm sd=2.5 n=100
<p>reported but not extracted: Pelvic pain, pelvic pressure, urinary symptoms, Lumber pain, Rectal pain, Dyspareunia, hypermenorrhoea, metrorrhagia, number with proliferative endometrium, haemoglobin</p>			
Source of funding	Not reported		
Comments	<p>Randomisation: Randomisation method not reported</p> <p>Allocation concealment: Staff not involved in the trial produced opaque sequentially numbered sealed envelopes containing the treatment allocation. Once the participant was enrolled in the trial the envelope was opened and the participant was assigned to the allocation within the envelope.</p> <p>Blinding: Not blinded.</p> <p>Other: Results reported based on available cases (no account for dropouts). Quality of life data were collected but not reported (results reported as 'similar' but no data given).</p>		

1 **Table 10: Carbonell 2013b**

Bibliographic reference	Carbonell JL, Acosta R, Perez Y et al. (2013) Safety and effectiveness of different dosage of mifepristone for the treatment of uterine fibroids: a double-blind randomized clinical trial. International Journal of Women's Health 5: 115-24													
Study type	Randomised controlled trial													
Aim	To evaluate the safety and improvement in quality of life using 10 mg and 5 mg daily doses of mifepristone for the treatment of uterine fibroids for 9 months.													
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Women of childbearing age 18+ - Symptomatic uterine fibroids <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Pregnancy or the desire to become pregnant. - Breastfeeding - hormonal contraception or any hormonal therapy in the last 3 months - signs or symptoms of pelvic inflammation, - adnexal tumours, - suspicion or diagnosis of cervical–uterine or ovarian cancer, - signs or symptoms of mental illness, - unexplained genital bleeding, - anaemia due to sickle-cell disease, - suffering from a serious illness, - antiprogesterone contraindications <p>Baseline characteristics (of randomised population)</p> <table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> <tr> <td>Age (mean,sd)</td><td>41.6 (5.7)</td><td>41.6 (4.8)</td></tr> <tr> <td>Race</td><td>not reported</td><td>not reported</td></tr> <tr> <td>Fibroid type</td><td>not reported</td><td>not reported</td></tr> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Mifepristone 5mg/d	Mifepristone 10mg/d	Age (mean,sd)	41.6 (5.7)	41.6 (4.8)	Race	not reported	not reported	Fibroid type	not reported	not reported
	Mifepristone 5mg/d	Mifepristone 10mg/d												
Age (mean,sd)	41.6 (5.7)	41.6 (4.8)												
Race	not reported	not reported												
Fibroid type	not reported	not reported												
Number of Patients	<table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> </table>			Mifepristone 5mg/d	Mifepristone 10mg/d									
	Mifepristone 5mg/d	Mifepristone 10mg/d												

Bibliographic reference	Carbonell JL, Acosta R, Perez Y et al. (2013) Safety and effectiveness of different dosage of mifepristone for the treatment of uterine fibroids: a double-blind randomized clinical trial. International Journal of Women's Health 5: 115-24		
	N (Randomised)	35	35
	Drop outs	Before end of treatment (4) 0-9 months follow up (15) 9-18 months follow up (7)	Before end of treatment (0) 0-9 months follow up (6) 9-18 months follow up (17)
Intervention	Mifepristone 5mg/d		
Comparison	Mifepristone 10mg/d (identical in appearance)		
Methods	Participants were randomised to receive 5mg/d or 10mg/d of mifepristone for 9 months.		
Length of follow up	9 months treatment period		
Location	Cuba. Secondary care setting.		
Outcomes measures and effect size	Quality of life – UFS-QOL test score (total – subscales not reported)		
		Mifepristone 5mg/d	Mifepristone 10mg/d
	Baseline	mean=62.5 sd=21.3 n=35	mean=60.7 sd=26.3 n=35
	End of 9 months treatment	mean=77.7 sd=20.3 n=31	mean=74.1 sd=25.9 n=34
	Fibroid volume (largest fibroid) evaluated by ultrasound		
	Mifepristone 5mg/d	Mifepristone 10mg/d	
Baseline	mean=115cm ³ sd=100 n=35	mean=263cm ³ sd=471 n=35	
End of 9 months	mean=55cm ³ sd=41	mean=90cm ³ sd=77	

Bibliographic reference		Carbonell JL, Acosta R, Perez Y et al. (2013) Safety and effectiveness of different dosage of mifepristone for the treatment of uterine fibroids: a double-blind randomized clinical trial. International Journal of Women's Health 5: 115-24	
	treatment	n=31	n=34
	9 months follow up	mean=130cm ³ sd=94 n=16	mean=196cm ³ sd=118 n=29
	18 months follow up	mean=169cm ³ sd=86 n=9	mean=255cm ³ sd=156 n=12
	Uterine volume evaluated by ultrasound		
		Mifepristone 5mg/d	Mifepristone 10mg/d
	Baseline	mean=542cm ³ sd=362 n=35	mean=866cm ³ sd=578 n=35
	End of 9 months treatment	mean=361cm ³ sd=175 n=31	mean=533cm ³ sd=570 n=35
	9 months follow up	mean=533cm ³ sd=452 n=16	mean=514cm ³ sd=369 n=29
	18 months follow up	mean=715cm ³ sd=433 n=9	mean=892cm ³ sd=412 n=12
	Endometrial hyperplasia (biopsy)		
		Mifepristone 5mg/d	Mifepristone 10mg/d
	6 months treatment	0/8	0/19
	9 months treatment	0/13	0/17
*not all women underwent biopsy			

Bibliographic reference	Carbonell JL, Acosta R, Perez Y et al. (2013) Safety and effectiveness of different dosage of mifepristone for the treatment of uterine fibroids: a double-blind randomized clinical trial. International Journal of Women's Health 5: 115-24		
	Endometrial thickness (surrogate for endometrial hyperplasia)		
		Mifepristone 5mg/d	Mifepristone 10mg/d
	Baseline	mean=6.2mm sd=1.7 n=35	mean=6.8mm sd=2.5 n=35
	End of 3 months treatment	mean=7.0mm sd=2.7 n=33	mean=9.2mm sd=4.5 n=35
	End of 6 months treatment	mean=7.4mm sd=2.6 n=31	mean=11.5mm sd=6.3 n=35
	End of 9 months treatment	mean=7.6mm sd=3.2 n=31	mean=10.8mm sd=6.6 n=35
	reported but not extracted: transaminases, hot flushes, amenorrhea, nausea, vomiting, fatigue, irregular bleeding, proliferative endometrium		
Source of funding	Liaphar S.A. supplied the study drugs free of charge.		
Comments	Randomisation: Computer-generated randomisation list. Allocation concealment: Staff not involved in the trial produced opaque sequentially numbered sealed envelopes containing the treatment allocation. Once the participant was enrolled in the trial the envelope was opened and the participant was assigned to the allocation within the envelope. Blinding: Double blind: patients and clinicians were blind to treatment allocation Other: Results reported based on available cases (no account for dropouts). Poorly matched in terms of fibroid and uterine volume at baseline (larger volume in 10mg/d group).		

1 **Table 11: Donnez 2012a, Williams 2012, Barlow 2014**

Bibliographic reference	<p>Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. <i>New England Journal of Medicine</i> 366: 409-20</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p> <p>Barlow DH, Lumsden MA, Fauser BC et al. (2014) Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. <i>Human Reproduction</i> 29: 480-9</p> <p>*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnez 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.</p>
Study type	Randomised controlled trial
Aim	To assess the efficacy and safety of oral ulipristal acetate for the treatment of symptomatic uterine fibroids before surgery. Known as the PEARL I study.
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Women aged 18 to 50 years - a score on the pictorial blood-loss assessment chart (PBAC, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding) higher than 100 during days 1 to 8 of menstruation - fibroid related anaemia, defined as a haemoglobin level of 10.2 g per decilitre or lower without macrocytosis - Uterine size equivalent to 16 weeks or less of gestation. - At least one fibroid that was 3cm or more in diameter, measured by ultrasound. - Body-mass index of 18 to 40. - Women were required to practice non-hormonal method(s) of contraception unless tubal ligation sterilization had been performed at least 2 months before the start of the study. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Fibroid greater than 10cm in diameter measured by ultrasound. - History of uterine surgery (except Caesarean section or cervical conization) - Endometrial ablation or uterine artery embolization - History of or current gynaecological cancer - Current endometrial hyperplasia - Haemoglobin ≤ 6 g/dL or any condition requiring immediate blood transfusion - Known hemoglobinopathy

Bibliographic reference	<p>Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. <i>New England Journal of Medicine</i> 366: 409-20</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p> <p>Barlow DH, Lumsden MA, Fauser BC et al. (2014) Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. <i>Human Reproduction</i> 29: 480-9</p> <p>*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnex 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.</p>																		
	<ul style="list-style-type: none">- Known severe coagulation disorder- Large uterine polyp (>2 cm)- One or more ovarian cysts ≥4 cm in diameter as measured by ultrasound- Previous or current treatment for fibroids with a selective progesterone receptor modulator or gonadotropin agonist- Treatment with agents known to affect hepatic cytochrome CYP3A4- Progestins, acetylsalicylic acid, mefenamic acid, anticoagulants, antifibrinolytic drugs or systemic glucocorticoid treatments. <p>Baseline characteristics (of intention to treat population)</p> <table><tr><th></th><th>Ulipristal acetate 5mg</th><th>Ulipristal acetate 10mg</th><th>Placebo</th></tr><tr><td>Age (mean,sd)</td><td>41.2 (5.9)</td><td>42.0 (5.6)</td><td>41.6 (5.6)</td></tr><tr><td>Race</td><td>White: 84 Asian: 11</td><td>White: 85 Asian: 9</td><td>White: 41 Asian: 7</td></tr><tr><td>Fibroid type</td><td>Submucosal 50/89 Intramural 58/89 Subserosal 25/89 Subserosal only 4/89</td><td>Submucosal 41/82 Intramural 59/82 Subserosal 33/82 Subserosal only 5/82</td><td>Submucosal 25/45 Intramural 36/45 Subserosal 9/45 Subserosal only 1/45</td></tr></table>				Ulipristal acetate 5mg	Ulipristal acetate 10mg	Placebo	Age (mean,sd)	41.2 (5.9)	42.0 (5.6)	41.6 (5.6)	Race	White: 84 Asian: 11	White: 85 Asian: 9	White: 41 Asian: 7	Fibroid type	Submucosal 50/89 Intramural 58/89 Subserosal 25/89 Subserosal only 4/89	Submucosal 41/82 Intramural 59/82 Subserosal 33/82 Subserosal only 5/82	Submucosal 25/45 Intramural 36/45 Subserosal 9/45 Subserosal only 1/45
	Ulipristal acetate 5mg	Ulipristal acetate 10mg	Placebo																
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	See outcome measures for baseline measures of reported outcomes																		
Number of Patients																			

Bibliographic reference	<p>Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. <i>New England Journal of Medicine</i> 366: 409-20</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p> <p>Barlow DH, Lumsden MA, Fauser BC et al. (2014) Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. <i>Human Reproduction</i> 29: 480-9</p> <p>*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnez 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.</p>			
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Placebo
	N (Randomised)	96	98	48
	N (ITT Analysis)	95	94	48
	Drop outs	6 Withdrew (5) Deviated from protocol (1)	5 Lost to follow up (1) Lack of efficacy (2) Withdrew (1) Deviated from protocol (1)	1 Lost to follow up (1)
Intervention 1	Ulipristal acetate 5mg/d			
Intervention 2	Ulipristal acetate 10mg/d			
Comparison	Placebo			
Methods	<p>Treatment was started during the first 4 days of menstruation. All participants also received iron supplements. After week 13 patients could undergo surgery according to the clinical judgement of the investigator:</p> <p>19/47 in the Placebo group underwent laparotomic hysterectomy (10), myomectomy (5) or uterine artery embolization (4)</p> <p>41/91 in the Ulipristal acetate 5mg group underwent laparotomic hysterectomy (11), vaginal or laparoscopic hysterectomy (7), myomectomy (12) or uterine artery embolization (11)</p> <p>49/92 in the Ulipristal acetate 10mg group underwent laparotomic hysterectomy (14), vaginal or laparoscopic hysterectomy (6), myomectomy (11) or uterine artery embolization (18)</p>			

Bibliographic reference	<p>Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. New England Journal of Medicine 366: 409-20</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. International Journal of Gynecological Pathology 31: 556-69</p> <p>Barlow DH, Lumsden MA, Fauser BC et al. (2014) Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. Human Reproduction 29: 480-9</p> <p>*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnex 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.</p>					
Length of follow up	13 weeks treatment duration, 6 months follow up for some outcomes (see outcome measures below)					
Location	38 academic research centres in six countries.					
Outcomes measures and effect size	Menstrual blood loss – number with pictorial blood loss assessment chart score < 75					
		Ulipristal Acetate 5mg		Ulipristal Acetate 10mg		Placebo
	Baseline (28 days)	0/95		0/94		0/48
	End (last 28 days of 13 week treatment)	86/94		86/93		9/48
	Menstrual blood loss - pictorial blood loss assessment chart score in preceding 28 days					
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Placebo	Difference UpA 5mg - Placebo	Difference UpA 10mg - Placebo
	Baseline (28 days)	median=386 IQR=235 to 627 n=95	median=330 IQR=235 to 537 n=94	median=376 IQR=241 to 608 n=48		
	Week 13 (end of treatment)	median=0 IQR=0 to 5 n=95	median=0 IQR=0 to 0 n=94	median=336 IQR=115 to 543 n=48		
	Change from	median=-329 IQR=-571 to -205	median=-326 IQR=-527 to -	median=-59 IQR=-216 to 58	median=-291 95%CI=-399 to -	median=-287 95%CI=-371 to -

Bibliographic reference	<p>Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. <i>New England Journal of Medicine</i> 366: 409-20</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p> <p>Barlow DH, Lumsden MA, Fauser BC et al. (2014) Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. <i>Human Reproduction</i> 29: 480-9</p> <p>*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnez 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.</p>					
	baseline (13 weeks)	n=95	226 n=94	n=48	194*	198*
	13 weeks follow up	median=260 IQR=101 to 459 n=50**	median=322 IQR=105 to 524 n=41**	median=322 IQR=105 to 52 n=26**		
	Change from baseline (13 weeks follow up)	median=-75 IQR=-247 to 73 n=50**	median=-94 IQR=-249 to 108 n=41**	median=-94 IQR=-249 to 108 n=26**	not reported	not reported
	25 weeks follow up	median=234 IQR=102 to 450 n=50**	median=174 IQR=46 to 321 n=41**	median=242 IQR=103 to 542 n=26**		
	Change from baseline (25 weeks follow up)	median=-81 IQR=-195 to 27 n=50**	median=-161 IQR=-256 to 13 n=41**	median=-113 IQR=-273 to 179 n=26**	not reported	not reported
*includes adjustment for multiple comparisons						

Bibliographic reference	Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. New England Journal of Medicine 366: 409-20					
	Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. International Journal of Gynecological Pathology 31: 556-69					
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	*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnex 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.					
	**only includes participants not undergoing surgery					
	Fibroid volume – total fibroid volume assessed by MRI					
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Placebo	Difference UpA 5mg - Placebo	Difference UpA 10mg - Placebo
	Baseline (28 days)	median=100.7cm ³ IQR=40.0 to 205.3	median=96.7cm ³ IQR=31.7 to 181.3	median=61.9cm ³ IQR=24.8 to 158.9		
	Change from baseline (13 weeks treatment)	median=-21.2% IQR=-41.2 to -1.1 n=95	median=-12.3% IQR=-39.1 to 4.30 n=94	median=3% IQR=-19.7 to 23.0 n=48	median=-22.6 95%CI=-36.1 to -8.2*	median=-18.2 95%CI=-33.0 to -5.2*
	13 weeks follow up	median=66.8 cm ³ IQR=18.6 to 151.4 n=49**	median=50.5cm ³ IQR=23.1 to 116.9 n=41**	median=39.0 cm ³ IQR=26.3 to 115.5 n=26**		
	Change from baseline	median= -4.1% IQR=-49.0 to 12.6 n=49**	median=-11.8% IQR=-46.0 to 3.0 n=41**	median= 2.9% IQR=-8.4 to 34.0 n=26**	not reported	not reported

Bibliographic reference	Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. New England Journal of Medicine 366: 409-20					
	Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. International Journal of Gynecological Pathology 31: 556-69					
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	*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnex 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.					
	(13 weeks follow up)					
	Change from baseline (13 weeks follow up)	median= 64.5 cm ³ IQR=23.7 to 164.2 n=49**	median=56 cm ³ IQR=27.0 to 121.2 n=41**	median= 49.0 cm ³ IQR=23.5 to 120.4 n=26**		
	25 weeks follow up	median= 6.6* IQR=-23.4 to 31.0 n=49**	median= -12.7% IQR=-43.8 to 15.3 n=41**	median= 9.7% IQR=-21.8 to 28.2 n=26**	not reported	not reported
	*includes adjustment for multiple comparisons **only includes participants not undergoing surgery					
Fibroid volume – number with >25% reduction compared with baseline						
		Ulipristal Acetate 5mg		Ulipristal Acetate 10mg		Placebo
	End of treatment (week 13)	35/85		33/80		8/45
Uterine volume – total fibroid volume assessed by MRI (not used in analysis as no confidence intervals reported or calculable)						
		Ulipristal Acetate	Ulipristal	Placebo	Difference UpA	Difference UpA

Bibliographic reference	<p>Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. New England Journal of Medicine 366: 409-20</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. International Journal of Gynecological Pathology 31: 556-69</p> <p>Barlow DH, Lumsden MA, Fauser BC et al. (2014) Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. Human Reproduction 29: 480-9</p> <p>*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnex 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.</p>					
		5mg median=325.6cm ³ IQR=212.6 to 453.3	Acetate 10mg median=337.6cm ³ IQR=236.1 to 502.8	median=318.8cm ³ IQR=216.0 to 496.3	5mg - Placebo not reported	10mg - Placebo not reported
	% change at end of 13 week treatment	medium=-12.0% IQR=-27.7 to 6.1	medium=-12.1% IQR=-28.3 to 2.9	median=5.9% IQR=-3.8 to 18.4		
	*includes adjustment for multiple comparisons					
	Uterine volume – number with >25% reduction compared with baseline					
		Ulipristal Acetate 5mg End of treatment (week 13) 30/88	Ulipristal Acetate 10mg 24/85	Placebo 3/47		
	Endometrial hyperplasia					
		Ulipristal Acetate 5mg Baseline 1/95 (complex hyperplasia with atypia) End of treatment 0/83	Ulipristal Acetate 10mg 0/98 0/81	Placebo 0/48 0/41		

Bibliographic reference	Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. New England Journal of Medicine 366: 409-20			
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	*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnex 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.			
	(week 13)			
	26 weeks Follow up *	0/63	0/63	1/31 (complex hyperplasia with atypia)
	*Only participants who did not undergo hysterectomy or endometrial ablation were included			
	Endometrial thickness (surrogate for endometrial hyperplasia)			
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Placebo
	Baseline	mean=6.77mm sd=3.05 n=95	mean=7.89mm sd=3.33 n=98	mean=8.25mm sd=3.51 n=48
	End of treatment (week 13)	mean=8.67 sd=6.12 n=95	mean=8.46 sd=5.01 n=98	mean=8.22 sd=3.46 n=48
	13 weeks follow up*	mean=7.4 sd=4.2 n=49	mean=7.9 sd=5.4 n=41	mean=7.9 sd=3.4 n=26
	26 weeks Follow up *	mean=7.9 sd=5.4 n=49	mean=8.46 sd=5.01 n=41	mean=8.22 sd=3.46 n=26
	*only included participants who did not undergo hysterectomy, myomectomy or uterine artery embolization			

Bibliographic reference	<p>Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. <i>New England Journal of Medicine</i> 366: 409-20</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p> <p>Barlow DH, Lumsden MA, Fauser BC et al. (2014) Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. <i>Human Reproduction</i> 29: 480-9</p> <p>*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnex 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.</p>											
	<p>Number undergoing surgical/radiological procedure</p> <table><tr><td></td><td>Ulipristal acetate 5mg/d</td><td>Ulipristal acetate 10mg/d</td><td>Placebo</td></tr><tr><td>13 weeks</td><td>41/91 laparotomic hysterectomy (11), vaginal or laparoscopic hysterectomy (7), myomectomy (12) or uterine artery embolization (11)</td><td>49/92 laparotomic hysterectomy (14), vaginal or laparoscopic hysterectomy (6), myomectomy (11) or uterine artery embolization (18)</td><td>19/47 laparotomic hysterectomy (10), myomectomy (5) or uterine artery embolization (4)</td></tr></table>					Ulipristal acetate 5mg/d	Ulipristal acetate 10mg/d	Placebo	13 weeks	41/91 laparotomic hysterectomy (11), vaginal or laparoscopic hysterectomy (7), myomectomy (12) or uterine artery embolization (11)	49/92 laparotomic hysterectomy (14), vaginal or laparoscopic hysterectomy (6), myomectomy (11) or uterine artery embolization (18)	19/47 laparotomic hysterectomy (10), myomectomy (5) or uterine artery embolization (4)
	Ulipristal acetate 5mg/d	Ulipristal acetate 10mg/d	Placebo									
13 weeks	41/91 laparotomic hysterectomy (11), vaginal or laparoscopic hysterectomy (7), myomectomy (12) or uterine artery embolization (11)	49/92 laparotomic hysterectomy (14), vaginal or laparoscopic hysterectomy (6), myomectomy (11) or uterine artery embolization (18)	19/47 laparotomic hysterectomy (10), myomectomy (5) or uterine artery embolization (4)									
	<p>reported but not extracted: Adverse events, pain assessment, measurement of discomfort questionnaire, amenorrhea, changes in hemoglobin, hematocrit, and ferritin levels, uterine cavity deformation, menstrual bleeding pattern, other endometrial changes</p>											
Source of funding	Study was funded by Preglem, who also designed the study. The data were collected by an independent company (ICON Clinical research) and analysed by another organisation (MDSL International). Barlow (2014) reported additional analysis on the same data set but did not receive any funding.											
Comments	<p>Randomisation: The investigator assigned patients to a study group with the use of a Web-integrated interactive voice-response system. Randomisation was in a 2:2:1 ratio (5mq. 10mq. placebo) and stratified according to</p>											

Bibliographic reference	<p>Donnez J, Tatarchuk TF, Bouchard P et al. (2012) Ulipristal acetate versus placebo for fibroid treatment before surgery. <i>New England Journal of Medicine</i> 366: 409-20</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p> <p>Barlow DH, Lumsden MA, Fauser BC et al. (2014) Individualized vaginal bleeding experience of women with uterine fibroids in the PEARL I randomized controlled trial comparing the effects of ulipristal acetate or placebo. <i>Human Reproduction</i> 29: 480-9</p> <p>*Note that Williams 2012 and Barlow 2014 report the same data as reported by Donnez 2012. No additional data is reported from Barlow 2014 in this evidence table, but the reference is included for completion.</p>
	<p>haematocrit level and race.</p> <p>Allocation concealment: Not described.</p> <p>Blinding: Described as 'double blind' – further details not specified.</p> <p>Other: All patients were eligible to undergo fibroid surgery after the end of the treatment period. Continuous data were reported not to meet the assumptions of parametric tests, and so medians and interquartile ranges were reported.</p>

1 Table 12: Donnez 2012b, Williams 2012

Bibliographic reference	<p>Donnez J, Tomaszewski J, Vazquez F et al. (2012) Ulipristal acetate versus leuprolide acetate for uterine fibroids. <i>New England Journal of Medicine</i> 366: 421-32</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p>
Study type	Randomised controlled trial
Aim	A non-inferiority trial to compare the efficacy and safety of oral ulipristal acetate and leuprolide acetate (a gonadotropin releasing hormone analogue) for the treatment of symptomatic uterine fibroids before surgery. Known as the PEARL II study.
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Women aged 18 to 50 years - a score on the pictorial blood-loss assessment chart (PBAC, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding) higher than 100 during days 1 to 8 of menstruation - Uterine size equivalent to 16 weeks or less of gestation.

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	<ul style="list-style-type: none"> - At least one fibroid that was 3cm or more in diameter, measured by ultrasound. - Body-mass index of 18 to 40. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Fibroid greater than 10cm in diameter measured by ultrasound. - History of uterine surgery (except Caesarean section or cervical conization) - Endometrial ablation or uterine artery embolization - History of or current gynaecological cancer - Current endometrial hyperplasia - Haemoglobin ≤ 6 g/dL or any condition requiring immediate blood transfusion - Known hemoglobinopathy - Known severe coagulation disorder - Large uterine polyp (>2 cm) - One or more ovarian cysts ≥ 4 cm in diameter as measured by ultrasound - Previous or current treatment for fibroids with a selective progesterone receptor modulator or gonadotropin agonist - Treatment with agents known to affect hepatic cytochrome CYP3A4 - Progestins, acetylsalicylic acid, mefenamic acid, anticoagulants, antifibrinolytic drugs or systemic glucocorticoid treatments. <p>Baseline characteristics (of per protocol population)</p> <table border="1"> <thead> <tr> <th></th><th>Ulipristal acetate 5mg</th><th>Ulipristal acetate 10mg</th><th>Leuprolide acetate</th></tr> </thead> <tbody> <tr> <td>Age (mean,sd)</td><td>40.1 (6.2)</td><td>40.7 (6.3)</td><td>40.3 (6.2)</td></tr> <tr> <td>Race</td><td>White (83) Black (9) Other (5)</td><td>White (88) Black (11) Other (4)</td><td>White (85) Black (9) Other (7)</td></tr> <tr> <td>Fibroid type</td><td>not reported</td><td>not reported</td><td>not reported</td></tr> </tbody> </table>				Ulipristal acetate 5mg	Ulipristal acetate 10mg	Leuprolide acetate	Age (mean,sd)	40.1 (6.2)	40.7 (6.3)	40.3 (6.2)	Race	White (83) Black (9) Other (5)	White (88) Black (11) Other (4)	White (85) Black (9) Other (7)	Fibroid type	not reported	not reported	not reported
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Age (mean,sd)	40.1 (6.2)	40.7 (6.3)	40.3 (6.2)																
Race	White (83) Black (9) Other (5)	White (88) Black (11) Other (4)	White (85) Black (9) Other (7)																
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	See outcome measures for baseline measures of reported outcomes					
Number of Patients		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Leuprolide acetate		
	N (Randomised)	98	104	101		
	N (Per protocol Analysis**)	93*	95*	93*		
	Drop outs	2 adverse event (1) lost to follow up (1)	3 adverse event (2) underwent surgery (1)	6 adverse event (6)		
	*Excluded patients with <80% compliance and major protocol violations. Safety analysis was based on all treated patients.					
Intervention 1	Ulipristal acetate 5mg/d + placebo saline injection once monthly					
Intervention 2	Ulipristal acetate 10mg/d + placebo saline injection once monthly					
Comparison	Placebo tablet once daily + 3.75mg of leuprolide acetate once monthly					
Methods	Treatment was started during the first 4 days of menstruation. All participants also received iron supplements. After week 13 patients could undergo surgery. Iron supplements were given at the discretion of the treating physician. Standardised sanitary materials were provided to allow assessment of menstrual blood loss.					
Length of follow up	13 weeks treatment duration, 6 months follow up (without further treatment) for endometrial safety data only					
Location	Academic research centres in six countries.					
Outcomes measures and effect size	Quality of life – UFS-Quoll questionnaire, health-related quality of life score					
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Leuprolide acetate	Difference UpA 5mg - leuprolide	Difference UpA 10mg - leuprolide
	Baseline					
	End of 13 week	mean=76.4	mean=81.5	mean=73.2	not reported	not reported

Bibliographic reference	Donnez J, Tomaszewski J, Vazquez F et al. (2012) Ulipristal acetate versus leuprolide acetate for uterine fibroids. New England Journal of Medicine 366: 421-32					
	Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. International Journal of Gynecological Pathology 31: 556-69					
	treatment	sd=23.2 n=93	sd=22.1 n=95	sd=23.0 n=93		
	Change from baseline	mean=23.7 sd=26.9 n=93	mean=24.8 sd=24.1 n=95	mean=23.2 sd=28.2 n=93	mean=2.5 95%ci=-7.3 to 12.3*	mean=5.6 95%ci=-3.9 to 15.1*
	*includes adjustment for multiple comparisons					
	Menstrual blood loss – number with pictorial blood loss assessment chart score < 75					
		Ulipristal Acetate 5mg		Ulipristal Acetate 10mg	Placebo	
	Baseline (28 days)	0/93		0/95	0/92	
	End (last 28 days of 13 week treatment)	84/93		93/95	82/92	
	Menstrual blood loss - pictorial blood loss assessment chart score in preceding 28 days					
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Leuprolide acetate	Difference UpA 5mg - leuprolide	Difference UpA 10mg - leuprolide
	Baseline	median=286 IQR=190 to 457 n=93	median=271 IQR=183 to 392 n=95	median=297 IQR=189 to 443 n=93		
	Week 13 (end of treatment)	median=0 IQR=0 to 2 n=93	median=0 IQR=0 to 0 n=95	median=0 IQR=0 to 4 n=93		
	Change from baseline (13 weeks)	median=-268	median=-268 IQR=-387 to	median=-274 IQR=-430 to -	median=6 95%CI=-54 to	median=3 95%CI=-45 to

Bibliographic reference	Donnez J, Tomaszewski J, Vazquez F et al. (2012) Ulipristal acetate versus leuprolide acetate for uterine fibroids. New England Journal of Medicine 366: 421-32					
	Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. International Journal of Gynecological Pathology 31: 556-69					
		IQR=-412 to -172 n=93	-179 n=95	161 n=93	63*	55*
	*includes adjustment for multiple comparisons					
	Fibroid volume – total fibroid volume of 3 largest fibroids					
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Leuprolide acetate	Ratio UpA 5mg /leuprolide	Ratio UpA 10mg /leuprolide
	Baseline	median=79.6 IQR=30.3 to 151.0 n=93	median=-47.6 IQR=24.1 to 110.6 n=93	median=-59.2 IQR=27.8 to 156.3 n=93		
	% change at end of 13 week treatment	median=-36 IQR=-58 to -11 n=93	median=-42 IQR=-69 to -14 n=95	median=-53 IQR=-69 to -35 n=93	not reported	not reported
	Ratio to baseline	geometric mean=0.66 sd not reported n=93	geometric mean=0.61 sd not reported n=95	geometric mean=0.54 sd not reported n=93	ratio=1.23 95%CI=0.99 to 1.52*	ratio=1.12 95%CI=0.91 to 1.38*
	*includes adjustment for multiple comparisons					
	Uterine volume –assessed by MRI					
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Leuprolide acetate	Difference UpA 5mg - leuprolide	Difference UpA 10mg - leuprolide
Baseline	median=199.4	median=197.8	median=199.9			

Bibliographic reference	Donnez J, Tomaszewski J, Vazquez F et al. (2012) Ulipristal acetate versus leuprolide acetate for uterine fibroids. New England Journal of Medicine 366: 421-32					
	Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. International Journal of Gynecological Pathology 31: 556-69					
		IQR=149.6 to 315.0 n=93	IQR=120.9 to 297.7 n=95	IQR=138.2 to 271.9 n=93		
	% change at end of 13 week treatment	median=-20 IQR=-40 to -3 n=93	median=-22 IQR=-45 to 0 n=95	median=-47 IQR=-57 to -35 n=93	not reported	not reported
	Ratio to baseline	geometric mean=0.84 sd not reported n=93	geometric mean=0.80 sd not reported n=93	geometric mean=0.57 sd not reported n=93	ratio=1.48 95%CI=1.25 to 1.74*	ratio=1.41 95%CI=1.19 to 1.66*
*includes adjustment for multiple comparisons						
Endometrial hyperplasia						
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Leuprolide acetate		
	Baseline	1/97 (simple hyperplasia without atypia)	0/103	0/101		
	End of treatment (week 13)	1/94 (simple hyperplasia without atypia)	0/98	0/95		
	Follow up (26 weeks follow up)*	0/63	0/67	0/64		
*Only participants who did not undergo hysterectomy or endometrial ablation were included. Denominator inferred by reviewer from numbers undergoing these procedures in each group						
Endometrial thickness (surrogate for endometrial hyperplasia)						
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Leuprolide acetate		
	Baseline	mean=8.9mm	mean=8.9mm	mean=9.0mm		

Bibliographic reference	<p>Donnez J, Tomaszewski J, Vazquez F et al. (2012) Ulipristal acetate versus leuprolide acetate for uterine fibroids. <i>New England Journal of Medicine</i> 366: 421-32</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p>			
		sd=4.2 n=97	sd=4.3 n=103	sd=3.9 n=101
	End of treatment (week 13)	mean=9.4mm sd=5.7 n=97	mean=10.7mm sd=5.9 n=103	mean=5.1mm sd=3.5 n=101
	Follow up (26 weeks follow up)*	mean=9.2mm sd=4.6 n=73	mean=8.1mm sd=3.6 n=78	mean=9.3mm sd=3.9 n=73
	*Only participants who did not undergo hysterectomy or myomectomy were included.			
	Number undergoing surgical/radiological procedure			
		Ulipristal acetate 5mg/d	Ulipristal acetate 10mg/d	Leuprolide acetate
	13 weeks treatment	50/95 11 Underwent laparotomic hysterectomy 7 Underwent vaginal or laparoscopic hysterectomy 30 Underwent myomectomy 2 Underwent other surgery	55/100 10 Underwent laparotomic hysterectomy 11 Underwent vaginal or laparoscopic hysterectomy 33 Underwent myomectomy 1 Underwent other surgery	52/95 14 Underwent laparotomic hysterectomy 7 Underwent vaginal or laparoscopic hysterectomy 29 Underwent myomectomy 2 Underwent other surgery
Source of funding		reported but not extracted: Adverse events not specified in protocol, serum estradiol, haemoglobin, pain score, other endometrial factors		
		Study was funded by Preglem, who also designed the study. The data were collected by an independent company (ICON Clinical research) and analysed by another organisation (MDSL International).		

Bibliographic reference	<p>Donnez J, Tomaszewski J, Vazquez F et al. (2012) Ulipristal acetate versus leuprolide acetate for uterine fibroids. <i>New England Journal of Medicine</i> 366: 421-32</p> <p>Williams AR, Bergeron C, Barlow DH et al. (2012) Endometrial morphology after treatment of uterine fibroids with the selective progesterone receptor modulator, ulipristal acetate. <i>International Journal of Gynecological Pathology</i> 31: 556-69</p>
Comments	<p>Randomisation: Randomisation was carried out using a Web-integrated interactive voice-response system. Randomisation was in a 1:1:1 ratio and stratified according to race./ethnic group</p> <p>Allocation concealment: The web integrated randomisation system transmitted allocations to a packaging company, which delivered medications to treatment centres.</p> <p>Blinding: Described as 'double blind' – further details not specified.</p> <p>Other: All patients were eligible to undergo fibroid surgery after the end of the treatment period. Continuous data were reported not to meet the assumptions of parametric tests, and so medians and interquartile ranges were reported. The study used a per protocol analysis – the justification was that an intention to treat analysis is non-conservative for a non-inferiority trial.</p>

1 Table 13: Donnez 2015, Donnez 2016

Bibliographic reference	<p>Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. <i>Fertility & Sterility</i> 103: 519-27</p> <p>Donnez J, Donnez O, Matule D et al. (2016) Long-term medical management of uterine fibroids with ulipristal acetate. <i>Fertility & Sterility</i> 105:166-173</p>
Study type	Randomised controlled trial
Aim	To investigate the efficacy and safety of repeated 12-week courses of 5 or 10 mg daily of ulipristal acetate for intermittent treatment of symptomatic uterine fibroids. Known as Pearl IV.
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Women aged 18 to 50 years - a score on the pictorial blood-loss assessment chart (PBAC, in which monthly scores range from 0 to >500, with higher numbers indicating more bleeding) higher than 100 during days 1 to 8 of menstruation - Uterine size equivalent to 16 weeks or less of gestation. - At least one fibroid that was 3cm or more in diameter, measured by ultrasound. - Body-mass index of 18 to 40. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - history of uterus surgery that would interfere with the study endpoints. Subjects who had a uterine artery embolization may be included in the study ≥6 months after the procedure.

Bibliographic reference	<p>Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertility & Sterility 103: 519-27</p> <p>Donnez J, Donnez O, Matule D et al. (2016) Long-term medical management of uterine fibroids with ulipristal acetate. Fertility & Sterility 105:166-173</p>													
	<ul style="list-style-type: none"> - history of or current uterus, cervix, ovarian or breast cancer. - history of endometrium hyperplasia or adenocarcinoma. - large uterine polyp (>2 cm). - severe coagulation disorder. - one or more ovarian cysts ≥ 4 cm diagnosed by ultrasound. - history of treatment for fibroids with a selective progesterone receptor modulator. - prohibited medication such as: Progestins, Acetylsalicylic acid, mefenamic acid, anticoagulants such as cumarins and/or antifibrinolytic drugs such as tranexamic, glucocorticoid. Gonadotropin Releasing Hormone (GnRH) agonist and antagonist - abnormal hepatic function at study entry. - positive pregnancy test at baseline, was nursing or planning a pregnancy during the course of the study. <p>Baseline characteristics (of intention to treat population)</p> <table border="1"> <thead> <tr> <th></th><th>Ulipristal acetate 5mg</th><th>Ulipristal acetate 10mg</th></tr> </thead> <tbody> <tr> <td>Age (mean,sd)</td><td>41.6 (5.4)</td><td>41.1 (5.1)</td></tr> <tr> <td>Race</td><td>Caucasian: 211 Black: 12 Other: 4 Not reported: 1</td><td>Caucasian: 214 Black: 8 Other: 1 Not reported: 0</td></tr> <tr> <td>Fibroid type</td><td>Not reported</td><td>Not reported</td></tr> </tbody> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Ulipristal acetate 5mg	Ulipristal acetate 10mg	Age (mean,sd)	41.6 (5.4)	41.1 (5.1)	Race	Caucasian: 211 Black: 12 Other: 4 Not reported: 1	Caucasian: 214 Black: 8 Other: 1 Not reported: 0	Fibroid type	Not reported	Not reported
	Ulipristal acetate 5mg	Ulipristal acetate 10mg												
Age (mean,sd)	41.6 (5.4)	41.1 (5.1)												
Race	Caucasian: 211 Black: 12 Other: 4 Not reported: 1	Caucasian: 214 Black: 8 Other: 1 Not reported: 0												
Fibroid type	Not reported	Not reported												
Number of Patients	<table border="1"> <thead> <tr> <th></th><th>Ulipristal Acetate 5mg</th><th>Ulipristal Acetate 10mg</th></tr> </thead> <tbody> <tr> <td>N (Randomised)</td><td>228</td><td>223</td></tr> <tr> <td>N (ITT)</td><td>228</td><td>223</td></tr> </tbody> </table>			Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	N (Randomised)	228	223	N (ITT)	228	223			
	Ulipristal Acetate 5mg	Ulipristal Acetate 10mg												
N (Randomised)	228	223												
N (ITT)	228	223												

Bibliographic reference	Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertility & Sterility 103: 519-27		
	Donnez J, Donnez O, Matule D et al. (2016) Long-term medical management of uterine fibroids with ulipristal acetate. Fertility & Sterility 105:166-173		
	Analysis)		
	Drop outs	34 Withdrew during 1st treatment (9) Withdrew between 1 st and 2 nd treatment (6) Withdrew during 2 nd treatment (5) Withdrew before post treatment biopsy visit (14)	30 Withdrew during 1st treatment (9) Withdrew between 1 st and 2 nd treatment (7) Withdrew during 2 nd treatment (4) Withdrew before post treatment biopsy visit (10)
Intervention	Ulipristal acetate 5mg/d		
Comparison	Ulipristal acetate 10mg/d		
Methods	Participants were randomised to receive 5 or 10mg/d ulipristal acetate for 4 12 week courses, separated by drug free intervals. Treatment was started during the first 4 days of menstruation. Subsequent courses were started with the second off-treatment menstruation.		
Length of follow up	4 * 12 week treatment periods, separated by drug free intervals (subsequent treatments started with second off treatment menstruation). First 2 treatment periods only reported by Donnez 2015 with additional treatment periods reported in Donnez 2016.		
Location	46 study sites across 11 countries		
Outcomes measures and effect size	Data reported for full analysis set when available (supplemental file also reports various per-protocol data sets)		
	Quality of life – UFS-Quoll total score		
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg
	Baseline	mean=56.9 sd=21.8 n=201	mean=56.8 sd=21.7 n=198
	End 1 st treatment	mean=80.1	mean=78.6

Bibliographic reference	<p>Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. <i>Fertility & Sterility</i> 103: 519-27</p> <p>Donnez J, Donnez O, Matule D et al. (2016) Long-term medical management of uterine fibroids with ulipristal acetate. <i>Fertility & Sterility</i> 105:166-173</p>		
	period (3 months treatment)	sd=18.2 n=182	sd=19.8 n=173
	Change from baseline (3 months treatment)	mean=25.1 sd=22.6 n=166	mean=21.5 sd=20.7 n=163
	Start of 2 nd treatment period	mean=69.1 sd=21.4 n=154	mean=70.1 sd=22.1 n=164
	Change from baseline (start 2 nd treatment)	mean=13.8 sd=19.7 n=136	mean=13.5 sd=19.0 n=151
	End of 2 nd treatment period	mean=78.5 sd=19.9 n=164	mean=77.3 sd=18.7 n=161
	Change from baseline (6 months treatment)	mean=20.7 sd=21.1 n=148	mean=20.1 sd=21.1 n=148
	Start of treatment 3	median=76.7 IQR=61.2 to 87.9 n=161	median=71.6 IQR=58.6 to 87.1 n=146
	End of treatment 3	median=84.5 IQR=67.7 to 94.0 n=164	median=81.9 IQR=65.5 to 94.0 n=163
	Start of treatment 4	median=78.9 IQR=58.6 to 92.2 n=146	median=76.7 IQR=61.2 to 91.4 n=151
	End of treatment	median=83.6	median=81.9

Bibliographic reference	Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. <i>Fertility & Sterility</i> 103: 519-27		
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	4	IQR=68.1 to 93.1 n=155	IQR=68.1 to 93.1 n=153
	Quality of life – UFS-Quoll symptom score		
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg
	Baseline	mean=48.2 sd=17.5 n=202	mean=49.3 sd=19.0 n=197
	End 1 st treatment period (3 months treatment)	mean=16.8 sd=15.3 n=182	mean=18.1 sd=18.0 n=173
	Change from baseline (3 months treatment)	mean=-32.3 sd=20.8 n=167	mean=-31.3 sd=21.0 n=163
	Start of 2 nd treatment period	mean=33.7 sd=18.9 n=154	mean=33.2 sd=20.8 n=164
	Change from baseline (start 2 nd treatment)	mean=-15.4 sd=20.5 n=137	mean=-15.9 sd=19.6 n=150
	End of 2 nd treatment period	mean=19.2 sd=17.7 n=165	mean=21.8 sd=18.6 n=161
	Change from baseline (6 months treatment)	mean=-27.9 sd=21.2 n=149	mean=-27.4 sd=23.5 n=147
	Start of treatment 3	median=28.1 IQR=18.8 to 40.6	median=31.3 IQR=18.8 to 46.9

Bibliographic reference	Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertility & Sterility 103: 519-27		
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		n=161	n=146
	End of treatment 3	median=15.6 IQR=9.4 to 25.0 n=164	median=15.6 IQR=6.3 to 28.1 n=163
	Start of treatment 4	median=25.0 IQR=15.6 to 40.6 n=146	median=25.0 IQR=12.5 to 43.8 n=151
	End of treatment 4	median=15.6 IQR=6.3 to 28.1 n=155	median=15.6 IQR=6.3 to 28.1 n=153
	Menstrual blood loss - pictorial blood loss assessment chart score in preceding 28 days		
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg
			Difference (10mg/d vs 5mg/d)
	Baseline (28 days)	median=224 IQR=148 to 357 n=228	median=215 IQR=151 to 373 n=223
	End of 1st 12 week treatment	median=123 IQR=45 to 313 n=172	median=129 IQR=56 to 285 n=156
	%Change from baseline (end of 1st treatment)	median=-87% IQR=-167 to 13 n=167	median=-85% IQR=-209 to -12 n=151
			median=-13% 95%CI=-54 to 28 Wilcoxon rank sum test: p=0.55
	End of 2nd treatment	median=92 IQR=44 to 243 n=159	median=99 IQR=37 to 202 n=152

Bibliographic reference	Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. <i>Fertility & Sterility</i> 103: 519-27			
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	%Change from baseline (1 st menses after 2 nd treatment)	median=-95% IQR=-216 to 9 n=152	median=-110% IQR=-236 to -50 n=146	median=-28 95%CI =-65 to 6 Wilcoxon rank sum test: p=0.10
	Change from baseline (1 st menses after 4 th treatment)	median=-118% IQR=-243 to -45 n=not reported	median=-121% IQR=-261 to -52 n=not reported	median=-11 95%CI=-49 to 26 Wilcoxon rank sum test: p=0.56
	Fibroid volume –volume of largest 3 fibroids assessed by MRI (not used for analysis because difference values appear inconsistent with data for each group, and no details are provided on how these were derived)			
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Difference
	Baseline	median=42.6cm ³ IQR=24.0 to 94.2 n=228	median=43.6 cm ³ IQR=27.3 to 117.3 n=223	
	Change from baseline (%) after 1 st menses after treatment period 1	median=-38% IQR=-60.3 to -14.3 n=207	median=-38.2% IQR=-60.3 to -15.0 n=206	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.91 95%CI=0.8 to 1.03
	Change from baseline (%) end treatment period 2	median=-54.1% IQR=-74.6 to -33.0 n=197	median=-58.0% IQR=-74.1 to -36.3 n=200	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.89 95%CI=0.75 to 1.07
	Change from baseline (%) after 1 st menses after treatment period 2	median=-53.8% IQR=-77.1 to -23.4 n=188	median=-58.1% IQR=-77.0 to -32.9 n=192	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.83 95%CI=0.69 to 1.01
Change from baseline (%) after	median=-60.8%	median=-64.4%	ratio (10mg ratio to baseline/5mg ratio to	

Bibliographic reference	Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertility & Sterility 103: 519-27			
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	1 st menses after treatment period 3	IQR=(-76.3 to -25.5) n=not reported	IQR=-80.9 to -42.3 n=not reported	baseline)=0.85 95%CI=0.69 to 1.04
	Change from baseline (%) after 1 st menses after treatment period 4	median=-67.0% IQR=-85.6 to -35.1 n=not reported	median=-70.4% IQR=-88.0 to -41.7 n=not reported	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.84 95%CI=0.65 to 1.08
	Fibroid volume –number with volume reduction>=25%			
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	
	After 1 st menses after treatment period 1	129/207	137/206	
	End treatment period 2	158/197	166/200	
	After 1 st menses after treatment period 2	139/188	152/192	
	After 1 st menses after treatment period 3	130/173	147/177	
	After 1 st menses after treatment period 4	125/160	128/159	
	Uterine volume – total fibroid volume assessed by MRI (not used for analysis because difference values appear inconsistent with data for each group, and no details are provided on how these were derived)			
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	Difference
	Baseline	median=176.9cm ³ IQR=113.1 to 269.8 n=228	median=175.2cm ³ IQR=116.6 to 267.6 n=223	
	Change from baseline (%)	median=-13.3% IQR=-28.5 to 8.2	median=-13.0% IQR=-29.5 to 3.5	ratio (10mg ratio to baseline/5mg ratio to

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	Donnez J, Donnez O, Matule D et al. (2016) Long-term medical management of uterine fibroids with ulipristal acetate. Fertility & Sterility 105:166-173			
	after 1 st menses after treatment period 1	n=214	n=211	baseline)=0.99 95%CI=0.92 to 1.05
	Change from baseline (%) end treatment period 2	median=-23.6% IQR=-40.9 to -4.4 n=205	median=-25.5% IQR=-44.7 to -5.9 n=203	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.96 95%CI=0.88 to 1.04
	Change from baseline (%) after 1 st menses after treatment period 2	median=-20.38% IQR=-35.1 to 2.6 n=194	median=-21.9% IQR=-41.5 to 0.4 n=196	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.95 (ratio) 95%CI=0.88 to 1.03
	Change from baseline (%) after 1 st menses after treatment period 3	median=-19.1% IQR=-37.4 to 4.2 n=not reported	median=-20.9% IQR=-39.9 to 5.7 n=not reported	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.975 (ratio) 95%CI=0.895 to 1.06
	Change from baseline (%) end treatment period 4	median=-25.1% IQR=-42.9 to -1.2 n=not reported	median=-30.7% IQR=-51.0 to -1.5 n=not reported	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.936 (ratio) 95%CI=0.851 to 1.03
	Change from baseline (%) after 1 st menses after treatment period 4	median=-19.7% IQR=-43.5 to 3.9 n=not reported	median=-23.0% IQR=-45.8 to -0.8 n=not reported	ratio (10mg ratio to baseline/5mg ratio to baseline)=0.964 (ratio) 95%CI=0.875 to 1.06
	Uterine volume –number with volume reduction>=25%			
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg	
After 1 st menses after treatment period 1		63/214	66/211	

Bibliographic reference	Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertility & Sterility 103: 519-27		
	Donnez J, Donnez O, Matule D et al. (2016) Long-term medical management of uterine fibroids with ulipristal acetate. Fertility & Sterility 105:166-173		
	End treatment period 2	98/205	103/203
	After 1st menses after treatment period 2	90/194	90/196
	After 1st menses after treatment period 3	74/182	84/182
	End treatment period 4	85/170	97/171
	Endometrial hyperplasia		
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg
	Baseline	0/219	0/203
	End treatment course 2 (post menses following)	1/178	2/182
	Endometrial thickness (surrogate for endometrial hyperplasia)		
		Ulipristal Acetate 5mg	Ulipristal Acetate 10mg
	Baseline	mean=8.4 sd=3.9 n=225	mean=8.4 sd=3.9 n=220
	After 1st menses after treatment period 1	mean=8.8 sd=4.3 n=214	mean=9.5 sd=4.8 n=207
	End treatment period 2	mean=8.7 sd=4.9 n=207	mean=7.9 sd=4.4 n=200
	After 1st menses after treatment period 2	mean=8.5 sd=3.8	mean=8.1 sd=4.3

Bibliographic reference	Donnez J, Hudecek R, Donnez O et al. (2015) Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. <i>Fertility & Sterility</i> 103: 519-27		
	Donnez J, Donnez O, Matule D et al. (2016) Long-term medical management of uterine fibroids with ulipristal acetate. <i>Fertility & Sterility</i> 105:166-173		
		n=192	n=193
	After 1 st menses after treatment period 3	median=8.0 IQR=6 to 11 n=not reported	median=7.0 IQR=5.0 to 9.0 n=not reported
	End treatment period 4	median=7.0 IQR=5.0 to 9.0 n=not reported	median=7.0 IQR=5.0 to 9.0 n=not reported
	After 1 st menses after treatment period 4	median=7.0 IQR=5.0 to 9.0 n=not reported	median=7.0 IQR=5.0 to 9.0 n=not reported
	reported but not extracted: amenorrhea, 'controlled bleeding', pain, adverse events not specified in review protocol, laboratory results, endometrial thickness >16 mm		
Source of funding	Study was funded by Preglem, who also designed the study. The data were collected by an independent company (ICON Clinical research) and analysed by another organisation (CROS NT).		
Comments	Randomisation: Randomisation method not described Allocation concealment: Not described explicitly – reported that used a web-integrated voice response system. Blinding: Described as 'double blind' – also states that pathologists assessing endometrial biopsies were blind to treatment allocation and visit number. Other: All randomised and treated patients were included in the analysis (data reported here is for full analysis set – other analysis sets reported in online supplemental data file).		

1 Table 14: Eisinger 2003, Eisinger 2005

Bibliographic reference	Eisinger SH, Meldrum S, Fiscella K et al. (2003) Low-dose mifepristone for uterine leiomyomata. <i>Obstetrics & Gynecology</i> 101: 243-50
	Eisinger SH, Bonfiglio T, Fiscella K et al. (2005) Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. <i>Journal of Minimally Invasive Gynecology</i> 12: 227-33
Study type	Randomised controlled trial

Bibliographic reference	Eisinger SH, Meldrum S, Fiscella K et al. (2003) Low-dose mifepristone for uterine leiomyomata. <i>Obstetrics & Gynecology</i> 101: 243-50 Eisinger SH, Bonfiglio T, Fiscella K et al. (2005) Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. <i>Journal of Minimally Invasive Gynecology</i> 12: 227-33									
Aim	To compare the effect of 5 and 10mg of mifepristone on uterine fibroid size and symptoms.									
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none">- Premenopausal- Active symptoms relating to fibroids.- Satisfy American College of Obstetricians and Gynaecologists criteria for hysterectomy or myomectomy- Uterine volume of >300cc by ultrasonography- Good general health- Agreement to use a non-hormonal method of contraception <p>Exclusion criteria:</p> <ul style="list-style-type: none">- Pregnancy or actively trying to become pregnant- Low ovarian reserve- Breast feeding- Adnexal masses- Tenderness indicating further evaluation- Abnormal or unexplained uterine bleeding- Diagnosed or suspected uterine, cervical or ovarian cancer- Significant mental disorder- Health problems contraindicating mifepristone <p>Additional exclusion criteria for further 6 months treatment:</p> <ul style="list-style-type: none">- Endometrial hyperplasia (assessed by biopsy at end of the 1st 6 months of treatment)- Persistently elevated hepatic enzymes- Poor adherence to the protocol <p>Baseline characteristics (of intention to treat population)</p> <table><tr><td></td><td>Mifepristone 5mg/d</td><td>Mifepristone 10mg/d</td></tr><tr><td>Age (mean,sd)</td><td>43.9 (5.1)</td><td>41.1 (5.3)</td></tr><tr><td>Race</td><td colspan="2">Not reported separately across groups: White: 13</td></tr></table>		Mifepristone 5mg/d	Mifepristone 10mg/d	Age (mean,sd)	43.9 (5.1)	41.1 (5.3)	Race	Not reported separately across groups: White: 13	
	Mifepristone 5mg/d	Mifepristone 10mg/d								
Age (mean,sd)	43.9 (5.1)	41.1 (5.3)								
Race	Not reported separately across groups: White: 13									

Bibliographic reference	Eisinger SH, Meldrum S, Fiscella K et al. (2003) Low-dose mifepristone for uterine leiomyomata. <i>Obstetrics & Gynecology</i> 101: 243-50		
	Eisinger SH, Bonfiglio T, Fiscella K et al. (2005) Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. <i>Journal of Minimally Invasive Gynecology</i> 12: 227-33		
		Black: 5 Hispanic: 1 Asian:1	
	Fibroid type	not reported	not reported
	See outcome measures for baseline measures of reported outcomes		
Number of Patients			
		Mifepristone 5mg/d	Mifepristone 10mg/d
	N (Randomised)	20	20
	N (ITT Analysis)	20	20
	Drop outs (first 6 months of treatment)	2 Lost to follow up (2)	0
	Drop outs (second 6 months of treatment)	7	10
Intervention	Mifepristone 5mg/d		
Comparison	Mifepristone 10mg/d		
Methods	Women were randomised to receive either 5mg or 10mg of mifepristone per day for 6 months.		
Length of follow up	6 months treatment duration + additional 6 months treatment on invitation if did not meet further exclusion criteria		
Location	USA, secondary care setting		
Outcomes measures and effect size	Menstrual blood loss – least squares mean menstrual blood loss index. Women were asked to classify blood loss each day on a scale of 0-5 (none, spotting, light, normal, heavy, very heavy. Values were summed for the month preceding the measurement point.		
		Mifepristone 5mg/d	Mifepristone 10mg/d

Bibliographic reference	<p>Eisinger SH, Meldrum S, Fiscella K et al. (2003) Low-dose mifepristone for uterine leiomyomata. <i>Obstetrics & Gynecology</i> 101: 243-50</p> <p>Eisinger SH, Bonfiglio T, Fiscella K et al. (2005) Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. <i>Journal of Minimally Invasive Gynecology</i> 12: 227-33</p>		
	Baseline	mean=22* 95%CI=18 to 26* n=20	mean=22.5* 95%CI=18.5 to 26.5* n=20
	3 months treatment	mean=2* 95%CI=-3 to 7* sd=10.68** n=20	mean=5* 95%CI=2 to 8* sd=6.41** n=20
	6 months treatment	mean=11* 95%CI=5.5 to 16.5* sd=11.75** n=20	mean=5.5* 95%CI=0.5 to 11* sd=11.22** n=20
	<p>*Estimated by reviewer from graph ** calculated by reviewer</p>		
	Uterine volume – assessed by ultrasound		
	Baseline	Mifepristone 5mg/d	Mifepristone 10mg/d
		mean=833 95%CI=748 to 918 sd=195.5* n=20	mean=850 95%CI= 762 to 938 sd=196.6* n=20
		2 months treatment (change from baseline) mean=-175 95%CI=-266 to -83* sd=195.51* n=20	mean=-207 95%CI=-299 to -115 sd=196.6* n=20
	6 months treatment (change from baseline)	mean=-400 95%CI=-487 to -312 sd=187.0* n=20	mean=-416 95%CI=-506 to -325 sd=193.4* n=20

Bibliographic reference	<p>Eisinger SH, Meldrum S, Fiscella K et al. (2003) Low-dose mifepristone for uterine leiomyomata. <i>Obstetrics & Gynecology</i> 101: 243-50</p> <p>Eisinger SH, Bonfiglio T, Fiscella K et al. (2005) Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. <i>Journal of Minimally Invasive Gynecology</i> 12: 227-33</p>									
	<p>*calculated by reviewer</p> <p>Uterine hyperplasia (simple hyperplasia identified on biopsy)</p> <table><tr><td></td><td>Mifepristone 5mg/d</td><td>Mifepristone 10mg/d</td></tr><tr><td>6 months treatment</td><td>4/16*</td><td>6/20</td></tr><tr><td>12 months treatment</td><td>0/11**</td><td>1/10**</td></tr></table> <p>*Biopsy was not possible in 3 participants, 1 failed to attend</p> <p>**hyperplasia at the end of the first 6 months was an exclusion criterion for embarking on the 2nd 6 months of treatment.</p> <p>reported but not extracted: Pelvic pain, pelvic pressure, bladder pressure, urinary frequency, lower back pain, rectal pain, pain with intercourse, hot flashes, headache, nausea, vomiting, mood swings, diarrhoea, decreased libido, weakness, fatigue, nervousness, hepatic enzymes, amenorrhea, Uterine volume data given for subset (<50% of women) but unclear whether error bars on graph represent confidence intervals, standard deviations or other measure. Individual uterine volume data for a subset of women after the end of treatment is reported (9 women, no summary statistics).</p>		Mifepristone 5mg/d	Mifepristone 10mg/d	6 months treatment	4/16*	6/20	12 months treatment	0/11**	1/10**
	Mifepristone 5mg/d	Mifepristone 10mg/d								
6 months treatment	4/16*	6/20								
12 months treatment	0/11**	1/10**								
Source of funding	David and Lucille Packard foundation									
Comments	<p>Randomisation: Randomisation was using a table of randomly computed numbers.</p> <p>Allocation concealment: Assignment was made by the study pharmacist (independently of the investigators) but allocation was not concealed.</p> <p>Blinding: Unblinded.</p> <p>Other: Intention to treat analysis used for efficacy data within first 6 month period : missing data imputed (last observation carried forward). Data for 12 months treatment are for available cases only.</p>									

1

2 **Table 15: Engman 2009**

Bibliographic reference	Engman M, Granberg S, Williams AR et al. (2009) Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. Human Reproduction 24: 1870-9													
Study type	Randomised controlled trial													
Aim	To investigate the effectiveness of mifepristone for fibroids.													
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Healthy non-pregnant women - Referred to outpatients clinic for fibroid-related problems (e.g. menorrhagia, pressure related symptoms from bladder or bowel or a considered risk for pregnancy complications) indicating surgical intervention <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Steroid hormonal therapy in the last 3 months before recruitment. - History of breast cancer or other malignancy - Bleeding not possible to control with tranexamic acid and iron medication (Implicating need for urgent surgical treatment) - Abnormal mammogram and breast biopsy at baseline investigation - adnexal abnormality, or suspicion of leiomyosarcoma upon transvaginal ultrasound examination - abnormal FSH and LH-levels or any other hormonal dysfunction of clinical significance; laboratory findings that would give suspicion of blood, liver or renal dysfunction - Abnormal PAP smear at screening - Any other contraindication to the use of mifepristone <p>Baseline characteristics (of randomised population)</p> <table border="1"> <thead> <tr> <th></th><th>Mifepristone 25mg/d</th><th>Placebo</th></tr> </thead> <tbody> <tr> <td>Age (mean,sd)</td><td>40.8 (4.7)</td><td>40.9 (7.6)</td></tr> <tr> <td>Race</td><td>not reported</td><td>not reported</td></tr> <tr> <td>Fibroid type</td><td>not reported</td><td>not reported</td></tr> </tbody> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Mifepristone 25mg/d	Placebo	Age (mean,sd)	40.8 (4.7)	40.9 (7.6)	Race	not reported	not reported	Fibroid type	not reported	not reported
	Mifepristone 25mg/d	Placebo												
Age (mean,sd)	40.8 (4.7)	40.9 (7.6)												
Race	not reported	not reported												
Fibroid type	not reported	not reported												
Number of Patients	<table border="1"> <thead> <tr> <th></th><th>Mifepristone 25mg/d</th><th>Placebo</th></tr> </thead> <tbody> <tr> <td>N</td><td>14</td><td>16</td></tr> </tbody> </table>			Mifepristone 25mg/d	Placebo	N	14	16						
	Mifepristone 25mg/d	Placebo												
N	14	16												

Bibliographic reference	Engman M, Granberg S, Williams AR et al. (2009) Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. Human Reproduction 24: 1870-9		
	(Randomised)		
	N (Available case analysis)	14	14
	Drop outs	0	2 Discontinued (2)* *due to elevated FSH and heavy bleeding in need of immediate surgery
Intervention	Mifepristone 50mg taken every other day (25mg/d)		
Comparison	Placebo: B vitamin tablets take every other day (visually identical to the mifepristone tablets)		
Methods	All participants were scheduled for surgery at the end of the trial. Treatment began on the first day of the menstrual cycle, and was continued for 3 months (ending the day before scheduled surgery).		
Length of follow up	3 month treatment duration		
Location	Sweden, Secondary care setting (patients referred for fibroid-related problems)		
Outcomes measures and effect size	Menstrual blood loss – number of bleeding days per 4 weeks – data not used in analysis as 95% confidence intervals not reported or possible to derive		
		Mifepristone 25mg/d	Placebo
	Weeks 1-4 of treatment	median=7 days range=4 to10 IQR=5 to 8* n=16	median=7.5 days range=2 to19 IQR=4 to 13* n=14
	Weeks 9-12 of treatment	median=0 days range=0 to 0 IQR=0 to 0* n=14	median=3 days range=0 to 23 IQR=1 to 10* n=14
	*Estimated by reviewer from graph		
	Fibroid volume – total fibroid volume assessed by ultrasound		
		Mifepristone 25mg/d	Placebo
	Baseline	median=161 ml	median=134 ml

Bibliographic reference	Engman M, Granberg S, Williams AR et al. (2009) Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. Human Reproduction 24: 1870-9		
		IQR= n=14	IQR=53 to 196 n=16
	End of study (12 weeks treatment)	median=106 ml IQR=52 to 205 n=12	median=118 ml IQR=80 to 160 n=15
	Change from baseline	mean=-28% 95% CI=-48 to -8% sd=31.48** n=12	mean=6% 95% CI=-13 to 25 sd=34.31** n=15
	**calculated by reviewer		
	Fibroid volume – dominant fibroid volume assessed by ultrasound		
		Mifepristone 25mg/d	Placebo
	Baseline	median=137 ml IQR=111 to 163 n=14	median=97 ml IQR=42 to 192 n=16
	End of study (12 weeks treatment)	median=96 ml IQR=42 to 129 n=12	median=85 ml IQR=68 to 160 n=15
	Change from baseline	mean=-27% 95% CI=-47 to -8 n=12	mean=8% 95% CI=-10 to 26 n=15
	Uterine hyperplasia		
		Mifepristone 25mg/d	Placebo
	Baseline	0/8*	0/11*
	Time of surgery	0/8*	0/11*
	*Biopsy data not available for all participants		
	reported but not extracted: Breast biopsy results, side effects not specified in protocol, blood and parenchymatous		

Bibliographic reference	Engman M, Granberg S, Williams AR et al. (2009) Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. Human Reproduction 24: 1870-9
	safety parameters, endometrial biopsy non-physiological changes, endometrial biopsy immune histochemistry
Source of funding	Swedish Research Council, Karolinska Institutet, Stockholm city county
Comments	<p>Randomisation: Randomisation was via a computer-generated, randomized, double-blinded selection procedure.</p> <p>Allocation concealment: Randomisation was completed by the Karolinska University Hospital pharmacy, who also packed and coded the medication.</p> <p>Blinding: Patients and staff were blinded to treatment groups.</p> <p>Other: Women did not have to be of reproductive age for inclusion (unclear whether post-menopausal women were included). The trial was stopped early (due to clinic reorganisation).</p>

1 Table 16: Esteve 2012

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2012) Treatment of uterine myoma with 5 or 10mg mifepristone daily during 6 months, post-treatment evolution over 12 months: double-blind randomised clinical trial. European Journal of Obstetrics, Gynecology, & Reproductive Biology 161: 202-8
Study type	Randomised controlled trial
Aim	To evaluate the efficacy and safety of 5 mg and 10 mg mifepristone for the treatment of uterine fibroids for 6 months, with a further 12 81months follow up.
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Women of childbearing age, aged 18+ - Symptomatic uterine fibroids - Using non-hormonal contraception <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Pregnancy or the desire to become pregnant. - Breastfeeding - hormonal contraception or any hormonal therapy in the last 3 months - signs or symptoms of pelvic inflammation, - adnexal tumours, - abnormal or unexplained uterine bleeding - suspicion of malignant neoplasm - signs or symptoms of mental illness, - adrenal disease - sickle-cell disease

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2012) Treatment of uterine myoma with 5 or 10mg mifepristone daily during 6 months, post-treatment evolution over 12 months: double-blind randomised clinical trial. European Journal of Obstetrics, Gynecology, & Reproductive Biology 161: 202-8													
	<ul style="list-style-type: none"> - hepatic disease - renal disease - antiprogesterone contraindications <p>Baseline characteristics (of randomised population)</p> <table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> <tr> <td>Age (mean,sd)</td><td>41.1 (4.7)</td><td>41.3 (6.1)</td></tr> <tr> <td>Race</td><td>White (29) Black (31) Afro-Cuban (28)</td><td>White (28) Black (33) Afro-Cuban (27)</td></tr> <tr> <td>Fibroid type</td><td>not reported</td><td>not reported</td></tr> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Mifepristone 5mg/d	Mifepristone 10mg/d	Age (mean,sd)	41.1 (4.7)	41.3 (6.1)	Race	White (29) Black (31) Afro-Cuban (28)	White (28) Black (33) Afro-Cuban (27)	Fibroid type	not reported	not reported
	Mifepristone 5mg/d	Mifepristone 10mg/d												
Age (mean,sd)	41.1 (4.7)	41.3 (6.1)												
Race	White (29) Black (31) Afro-Cuban (28)	White (28) Black (33) Afro-Cuban (27)												
Fibroid type	not reported	not reported												
Number of Patients	<table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> <tr> <td>N (Randomised)</td><td>88</td><td>88</td></tr> <tr> <td>Drop outs</td><td>14 0-3 months treatment (2) 3-6 months treatment (4) 0-3 months follow up (3) 3-6 months follow up (2) 6-9 months follow up (1) 9-12 months follow up (2)</td><td>18 0-3 months treatment (3) 3-6 months treatment (7) 0-3 months follow up (3) 3-6 months follow up (1) 6-9 months follow up (1) 9-12 months follow up (3)</td></tr> </table>			Mifepristone 5mg/d	Mifepristone 10mg/d	N (Randomised)	88	88	Drop outs	14 0-3 months treatment (2) 3-6 months treatment (4) 0-3 months follow up (3) 3-6 months follow up (2) 6-9 months follow up (1) 9-12 months follow up (2)	18 0-3 months treatment (3) 3-6 months treatment (7) 0-3 months follow up (3) 3-6 months follow up (1) 6-9 months follow up (1) 9-12 months follow up (3)			
	Mifepristone 5mg/d	Mifepristone 10mg/d												
N (Randomised)	88	88												
Drop outs	14 0-3 months treatment (2) 3-6 months treatment (4) 0-3 months follow up (3) 3-6 months follow up (2) 6-9 months follow up (1) 9-12 months follow up (2)	18 0-3 months treatment (3) 3-6 months treatment (7) 0-3 months follow up (3) 3-6 months follow up (1) 6-9 months follow up (1) 9-12 months follow up (3)												
Intervention	Mifepristone 5mg/d													
Comparison	Mifepristone 10mg/d													
Methods	Participants were randomised to receive either 5 or 10mg of mifepristone for 6 months, and followed up for a further 12 months after treatment. Treatment was not synchronised with the menstrual cycle.													

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2012) Treatment of uterine myoma with 5 or 10mg mifepristone daily during 6 months, post-treatment evolution over 12 months: double-blind randomised clinical trial. European Journal of Obstetrics, Gynecology, & Reproductive Biology 161: 202-8																															
Length of follow up	6 month treatment period, 12 months follow up																															
Location	Cuba. Secondary care setting.																															
Outcomes measures and effect size⁸¹	Fibroid volume evaluated by ultrasound <table border="1"> <thead> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> </thead> <tbody> <tr> <td>Baseline</td><td>mean=133cm³ sd=176 n=74</td><td>mean=108cm³ sd=103 n=70</td></tr> <tr> <td>End of treatment (6 months)</td><td>mean=81cm³ sd=102 n=74</td><td>mean=56cm³ sd=61 n=70</td></tr> <tr> <td>12 months follow up</td><td>mean=138cm³ sd=117 n=74</td><td>mean=128cm³ sd=108 n=70</td></tr> </tbody> </table> Uterine volume evaluated by ultrasound <table border="1"> <thead> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> </thead> <tbody> <tr> <td>Baseline</td><td>mean=573cm³ sd=480 n=74</td><td>mean=544cm³ sd=353 n=70</td></tr> <tr> <td>End of treatment (6 months)</td><td>mean=417cm³ sd=271 n=74</td><td>mean=379cm³ sd=259 n=70</td></tr> <tr> <td>12 months follow up</td><td>mean=666cm³ sd=219 n=74</td><td>mean=596cm³ sd=299 n=70</td></tr> </tbody> </table> Endometrial thickness (surrogate for endometrial hyperplasia) <table border="1"> <thead> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Mifepristone 10mg/d</th></tr> </thead> <tbody> <tr> <td>Baseline</td><td>mean=6.4mm</td><td>mean=6.4mm</td></tr> </tbody> </table>			Mifepristone 5mg/d	Mifepristone 10mg/d	Baseline	mean=133cm ³ sd=176 n=74	mean=108cm ³ sd=103 n=70	End of treatment (6 months)	mean=81cm ³ sd=102 n=74	mean=56cm ³ sd=61 n=70	12 months follow up	mean=138cm ³ sd=117 n=74	mean=128cm ³ sd=108 n=70		Mifepristone 5mg/d	Mifepristone 10mg/d	Baseline	mean=573cm ³ sd=480 n=74	mean=544cm ³ sd=353 n=70	End of treatment (6 months)	mean=417cm ³ sd=271 n=74	mean=379cm ³ sd=259 n=70	12 months follow up	mean=666cm ³ sd=219 n=74	mean=596cm ³ sd=299 n=70		Mifepristone 5mg/d	Mifepristone 10mg/d	Baseline	mean=6.4mm	mean=6.4mm
	Mifepristone 5mg/d	Mifepristone 10mg/d																														
Baseline	mean=133cm ³ sd=176 n=74	mean=108cm ³ sd=103 n=70																														
End of treatment (6 months)	mean=81cm ³ sd=102 n=74	mean=56cm ³ sd=61 n=70																														
12 months follow up	mean=138cm ³ sd=117 n=74	mean=128cm ³ sd=108 n=70																														
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Baseline	mean=6.4mm	mean=6.4mm																														

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2012) Treatment of uterine myoma with 5 or 10mg mifepristone daily during 6 months, post-treatment evolution over 12 months: double-blind randomised clinical trial. European Journal of Obstetrics, Gynecology, & Reproductive Biology 161: 202-8		
		sd=2.4 n=74	sd=2.5 n=70
	End of treatment (6 months)	mean=9.5mm sd=4.7 n=74	mean=10.3mm sd=5.3 n=70
	12 months follow up	mean=6.1mm sd=2.1 n=74	mean=6.1mm sd=2.1 n=70
	reported but not extracted: pelvic pain, hypermenorrhoea, pelvic pressure, urinary symptoms, rectal or lumbar pain, dyspareunia, metrorrhagia		
Source of funding	Not reported		
Comments	<p>Randomisation: Randomisation was via a computer generated list.</p> <p>Allocation concealment: Sequentially numbered sealed envelopes contained the treatment allocation. Once the participant was enrolled in the trial the envelope was opened and the participant was assigned to the allocation within the envelope.</p> <p>Blinding: No details of blinding: presume unblinded due to method of treatment allocation.</p> <p>Other: Only report data on participants who completed treatment and follow up (dropouts not accounted for).</p>		

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2 Table 17: Esteve 2013

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2013) Mifepristone versus placebo to treat uterine myoma: a double-blind, randomized clinical trial. International Journal of Women's Health 5: 361-9
Study type	Randomised controlled trial
Aim	To evaluate the efficacy, safety, and quality of life of 5 mg mifepristone per day compared with a placebo in treating uterine fibroids.
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Women of childbearing age, aged 18+ - Symptomatic uterine fibroids requiring treatment to improve general condition before hysterectomy or myomectomy

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2013) Mifepristone versus placebo to treat uterine myoma: a double-blind, randomized clinical trial. International Journal of Women's Health 5: 361-9													
	<ul style="list-style-type: none">- Clinical indications for myomectomy or hysterectomy													
	Exclusion criteria: <ul style="list-style-type: none">- Pregnancy or the desire to become pregnant.- Breastfeeding- hormonal contraception or any hormonal therapy in the last 3 months- signs or symptoms of pelvic inflammation,- adnexal tumours,- suspicion or diagnosis of cervical–uterine or ovarian cancer,- signs or symptoms of mental illness,- unexplained genital bleeding,- anaemia due to sickle-cell disease,- suffering from a serious illness,- antiprogesterone contraindications													
	Baseline characteristics (of intention to treat population)													
		<table><tr><th></th><th>Mifepristone 5mg/d</th><th>Placebo</th></tr><tr><td>Age (mean,sd)</td><td>39.1 (6.6)</td><td>37.8 (6.6)</td></tr><tr><td>Race</td><td>White (22) Black (27) Afro-Cuban (13)</td><td>White (20) Black (26) Afro-Cuban (16)</td></tr><tr><td>Fibroid type</td><td>Not reported</td><td>Not reported</td></tr></table>		Mifepristone 5mg/d	Placebo	Age (mean,sd)	39.1 (6.6)	37.8 (6.6)	Race	White (22) Black (27) Afro-Cuban (13)	White (20) Black (26) Afro-Cuban (16)	Fibroid type	Not reported	Not reported
		Mifepristone 5mg/d	Placebo											
Age (mean,sd)	39.1 (6.6)	37.8 (6.6)												
Race	White (22) Black (27) Afro-Cuban (13)	White (20) Black (26) Afro-Cuban (16)												
Fibroid type	Not reported	Not reported												
	See outcome measures for baseline measures of reported outcomes													
Number of Patients	<table><tr><th></th><th>Mifepristone 5mg/d</th><th>Placebo</th></tr><tr><td>N (Randomised)</td><td>62</td><td>62</td></tr><tr><td>N (Available case Analysis)</td><td>58</td><td>47</td></tr></table>			Mifepristone 5mg/d	Placebo	N (Randomised)	62	62	N (Available case Analysis)	58	47			
	Mifepristone 5mg/d	Placebo												
N (Randomised)	62	62												
N (Available case Analysis)	58	47												

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2013) Mifepristone versus placebo to treat uterine myoma: a double-blind, randomized clinical trial. <i>International Journal of Women's Health</i> 5: 361-9		
	Drop outs*	4 Lack of efficacy (1) Fibroid expulsion (1) Adverse reaction (1) High arterial pressure (1)	15 Pregnancy (2) Fear of biopsy (1) Venous thrombosis (1) Fear of taking tablets (1) Burns (1) Lost to follow up (9)
	*Significantly greater number of dropouts in the placebo group		
Intervention	Mifepristone 5mg/d		
Comparison	Placebo (identical in shape size and colour)		
Methods	Participants were randomised to receive mifepristone or placebo for 3 months. There are no details about synchronising treatment with the menstrual cycle.		
Length of follow up	3 months treatment duration		
Location	Cuba, secondary care setting		
Outcomes measures and effect size	Quality of life: UFS-QOL test		
		Mifepristone 5mg	Placebo
	Symptom score Baseline	mean=49.0 sd=16.4 n=48	mean=43.2 sd=23.0 n=40
	Symptom score End (3 months treatment)	mean=29.3 sd=17.7 n=48	mean=41.6 sd=21.2 n=40
	Total score Baseline	mean=62.6 sd=20.75 n=48	mean=69.0 sd=20.5 n=40
	Total score End (3 months treatment)	mean=76.2 sd=23.4 n=48	mean=70.2 sd=22.0 n=40

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2013) Mifepristone versus placebo to treat uterine myoma: a double-blind, randomized clinical trial. International Journal of Women's Health 5: 361-9		
	Fibroid volume: Volume of largest fibroid measured by ultrasound		
		Mifepristone 5mg	Placebo
	Baseline	mean=125cm ³ sd=95 n=58	mean=119 cm ³ sd=96 n=47
	End (3 months treatment)	mean=88 cm ³ sd=79 n=58	mean=123 cm ³ sd=88 n=47
	Uterine volume: measured by ultrasound		
		Mifepristone 5mg	Placebo
	Baseline	mean=458 cm ³ sd=236 n=58	mean=428 cm ³ sd=211 n=47
	End (3 months treatment)	mean=354cc sd=202 n=58	mean=439 cm ³ sd=210 n=47
	Endometrial thickness (surrogate for endometrial hyperplasia)		
		Mifepristone 5mg	Placebo
	Baseline	mean=7.4mm sd=1.9 n=58	mean=7.4mm sd=2.0 n=47
	End (3 months treatment)	mean=10.3 sd=2.7 n=58	mean=8.4 sd=2.8 n=47
reported but not extracted: Pelvic pain, pelvic pressure, urinary symptoms, lumbar pain, rectal pain, dyspareunia,			

Bibliographic reference	Esteve JL, Acosta R, Perez Y et al. (2013) Mifepristone versus placebo to treat uterine myoma: a double-blind, randomized clinical trial. International Journal of Women's Health 5: 361-9
	hypermenorrhoea, metrorrhagia,, sex hormone levels, number with proliferative endometrium, number with progesterone modulator associated endometrial changes. Other quality of life subscales not in review protocol.
Source of funding	Not reported. The authors declared that there were no conflicts of interest.
Comments	<p>Randomisation: Treatment allocation was described as randomised, but details of randomisation method not provided.</p> <p>Allocation concealment: Staff not directly involved in the study prepared sealed opaque envelopes, each envelope containing a card indicating treatment allocation code.</p> <p>Blinding: Doctors and patients were blind to treatment allocation.</p> <p>Other: There was a significantly greater number of dropouts in the placebo group, and analysis was based on available cases completing treatment only. Not all participants completed the quality of life measure.</p>

1 Table 18: Fiscella 2006

Bibliographic reference	Fiscella K, Eisinger SH, Meldrum S et al. (2006) Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. Obstetrics & Gynecology 108: 1381-7
Study type	Randomised controlled trial
Aim	To assess the effect of 5mg/d mifepristone on fibroid-specific quality of life for women with symptomatic uterine fibroids.
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Aged 18 years or more - Premenopausal - At least moderately severe fibroid-related symptoms (>39 on the fibroid symptom quality of life subscale). - Total uterine volume (by ultrasound) of 160ml or more - At least one fibroid greater than 3cm in diameter. - Agreed to use barrier contraception and use other hormonal or surgical treatments during the course of the trial. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Used short-acting hormones in the past 3 months - Used gonadotrophin releasing hormone analogues or other long-acting hormonal medication in the past 6 months. - Pregnant or intending to become pregnant in the next 6 months. - Major medical morbidity or severe anaemia.

Bibliographic reference	Fiscella K, Eisinger SH, Meldrum S et al. (2006) Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. Obstetrics & Gynecology 108: 1381-7													
	Baseline characteristics (of intention to treat population) <table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Placebo</th></tr> <tr> <td>Age (mean,sd)</td><td>44.8 (6.2)</td><td>43.2 (4.7)</td></tr> <tr> <td>Race</td><td>African American: 11</td><td>African American: 11</td></tr> <tr> <td>Fibroid type</td><td>not reported</td><td>not reported</td></tr> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Mifepristone 5mg/d	Placebo	Age (mean,sd)	44.8 (6.2)	43.2 (4.7)	Race	African American: 11	African American: 11	Fibroid type	not reported	not reported
	Mifepristone 5mg/d	Placebo												
Age (mean,sd)	44.8 (6.2)	43.2 (4.7)												
Race	African American: 11	African American: 11												
Fibroid type	not reported	not reported												
Number of Patients	<table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Placebo</th></tr> <tr> <td>N (Randomised)</td><td>22</td><td>20</td></tr> <tr> <td>Drop outs</td><td>2 Reasons not reported</td><td>3 Reasons not reported</td></tr> </table>			Mifepristone 5mg/d	Placebo	N (Randomised)	22	20	Drop outs	2 Reasons not reported	3 Reasons not reported			
	Mifepristone 5mg/d	Placebo												
N (Randomised)	22	20												
Drop outs	2 Reasons not reported	3 Reasons not reported												
Intervention	Mifepristone 5mg/d													
Comparison	Placebo													
Methods	Women were randomised to receive mifepristone (5 mg/d) or placebo daily for 27 weeks.													
Length of follow up	26 weeks treatment duration													
Location	USA secondary care setting													
Outcomes measures and effect size	Quality of life –Uterine leiomyoma quality of life scale (total score) <table> <tr> <th></th><th>Mifepristone 5mg/d</th><th>Placebo</th></tr> <tr> <td>Baseline</td><td>mean=36* 95%CI=26 to 46* n=22</td><td>mean=41* 95%CI=31 to 51* n=20</td></tr> <tr> <td>3 months treatment</td><td>mean=84* 95%CI=73 to 95* sd=23.5** n=20</td><td>mean=52* 95%CI=41 to 63* sd=21.39** n=17</td></tr> <tr> <td>6 months treatment</td><td>mean=86* 95%CI=75 to 97*</td><td>mean=55* 95%CI=42 to 69*</td></tr> </table>			Mifepristone 5mg/d	Placebo	Baseline	mean=36* 95%CI=26 to 46* n=22	mean=41* 95%CI=31 to 51* n=20	3 months treatment	mean=84* 95%CI=73 to 95* sd=23.5** n=20	mean=52* 95%CI=41 to 63* sd=21.39** n=17	6 months treatment	mean=86* 95%CI=75 to 97*	mean=55* 95%CI=42 to 69*
	Mifepristone 5mg/d	Placebo												
Baseline	mean=36* 95%CI=26 to 46* n=22	mean=41* 95%CI=31 to 51* n=20												
3 months treatment	mean=84* 95%CI=73 to 95* sd=23.5** n=20	mean=52* 95%CI=41 to 63* sd=21.39** n=17												
6 months treatment	mean=86* 95%CI=75 to 97*	mean=55* 95%CI=42 to 69*												

Bibliographic reference	Fiscella K, Eisinger SH, Meldrum S et al. (2006) Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. <i>Obstetrics & Gynecology</i> 108: 1381-7		
		sd=23.5** n=20	sd=26.3** n=17
	*Estimated by reviewer from graph		
	**Calculated by reviewer		
	Menstrual blood loss –pictorial blood loss assessment used to assess blood loss, and each day assigned a score between 0 and 4 to indicate no, light, moderate or heavy flow. This was summed across the 1 month preceding the specified time point		
		Mifepristone 5mg/d	Placebo
	Baseline	mean=23* 95%CI= 19 to 27* sd=5.19*** n=22	mean=22.5* 95%CI=18.5 to 26.5* sd=8.55*** n=20
	3 months treatment	mean=3* 95%CI=-0.5 to 6.5** sd=7.48*** n=20	mean=17* 95%CI=12 to 22* sd=9.72*** n=17
	6 months treatment	mean=5.5 95%CI=1 to 10*8 sd=9.62*** n=20	mean=20* 95%CI=16 to 24* sd=7.78**** n=17
	*Estimated by reviewer from graph		
	**arises because confidence intervals are symmetric, not meaningful to have negative number		
***calculated by reviewer			
Uterine volume – measured by vaginal and abdominal ultrasound			
	Mifepristone 5mg/d	Placebo	
Baseline	mean=719 sd=663 n=22	mean=449 sd=236 n=20	
3 months	mean=-100*	mean=50*	

Bibliographic reference	Fiscella K, Eisinger SH, Meldrum S et al. (2006) Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. <i>Obstetrics & Gynecology</i> 108: 1381-7		
	treatment (change from baseline)	95%CI=-205 to 5* sd=224.4** n=20	95%CI=-60 to 160* sd=213.9 n=17
	6 months treatment (change from baseline)	mean=-200* 95%CI=-380 to -20* sd=384.6** n=20	mean=60* 95%CI=-130 to 250* sd=369.5** n=17
<p>*Estimated by reviewer from graph **calculated by reviewer</p> <p>reported but not extracted: Pain (McGill Pain questionnaire), haemoglobin levels, anaemia</p>			
Source of funding	National institute for child health and human development. Athenium laboratories supplied drugs at cost.		
Comments	<p>Randomisation: A random number generator was used for randomisation. Randomisation was in blocks of 4 stratified for quality of life score symptom severity at baseline.</p> <p>Allocation concealment: Assignments were placed in opaque sealed envelopes that were opened by the study pharmacist after enrolment. 19 out of 20 correctly guessed they were receiving mifepristone by the end of the study. 4 guessed that they were receiving the drug in the placebo group.</p> <p>Blinding: Only the study pharmacist was aware of treatment allocations.</p> <p>Other: Unclear how missing data were dealt with in the analysis – appears that analysis was based on available cases. Number of participants for each data point calculated by reviewer based on total number of dropout (except for baseline measure, to be conservative). Poorly matched for uterine volume at baseline (placebo group smaller volume).</p>		

1

2 Table 19: Kulshrestha 2013

Bibliographic reference	Kulshrestha V, Kriplani A, Agarwal N et al. (2013) Low dose mifepristone in medical management of uterine leiomyoma - an experience from a tertiary care hospital from north India. <i>Indian Journal of Medical Research</i> 137: 1154-62
Study type	Randomised controlled trial
Aim	To compare two doses (10mg/d and 25mg/d) of mifepristone for the treatment of uterine fibroids.
Patient characteristics	Inclusion criteria:

Bibliographic reference	Kulshrestha V, Kriplani A, Agarwal N et al. (2013) Low dose mifepristone in medical management of uterine leiomyoma - an experience from a tertiary care hospital from north India. Indian Journal of Medical Research 137: 1154-62													
	<ul style="list-style-type: none"> - Aged 20 to 50 years - Single or multiple fibroids - Symptomatic fibroids or largest fibroid >5cm diameter on ultrasound <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - Uterine size equivalent to a 20 wk pregnancy - Fibroids > 15cm diameter - Grade 0 submucosal fibroids - Renal or hepatic dysfunction - Suspected adenomyosis - Current genital infection - Endometrial hyperplasia with atypia - Hormonal medication within the last 3 months - Women desiring pregnancy <p>Baseline characteristics (of intention to treat population)</p> <table> <tr> <th></th><th>Mifepristone 10mg/d</th><th>Mifepristone 25mg/d</th></tr> <tr> <td>Age (mean,sd)</td><td>36.2 (7.15)</td><td>35.6 (7.42)</td></tr> <tr> <td>Race</td><td>not reported</td><td>not reported</td></tr> <tr> <td>Fibroid type</td><td>not reported</td><td>not reported</td></tr> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Mifepristone 10mg/d	Mifepristone 25mg/d	Age (mean,sd)	36.2 (7.15)	35.6 (7.42)	Race	not reported	not reported	Fibroid type	not reported	not reported
	Mifepristone 10mg/d	Mifepristone 25mg/d												
Age (mean,sd)	36.2 (7.15)	35.6 (7.42)												
Race	not reported	not reported												
Fibroid type	not reported	not reported												
Number of Patients	<table> <tr> <th></th><th>Mifepristone 10mg/d</th><th>Mifepristone 25mg/d</th></tr> <tr> <td>N (Randomised)</td><td>75</td><td>75</td></tr> <tr> <td>Drop outs</td><td>During treatment (2) 0-3 months follow up (4) 3-6 months follow up (5)</td><td>During treatment (5) 0-3 months follow up (5) 3-6 months follow up (5)</td></tr> </table>			Mifepristone 10mg/d	Mifepristone 25mg/d	N (Randomised)	75	75	Drop outs	During treatment (2) 0-3 months follow up (4) 3-6 months follow up (5)	During treatment (5) 0-3 months follow up (5) 3-6 months follow up (5)			
	Mifepristone 10mg/d	Mifepristone 25mg/d												
N (Randomised)	75	75												
Drop outs	During treatment (2) 0-3 months follow up (4) 3-6 months follow up (5)	During treatment (5) 0-3 months follow up (5) 3-6 months follow up (5)												
Intervention	Mifepristone 10mg/d													

Bibliographic reference	Kulshrestha V, Kriplani A, Agarwal N et al. (2013) Low dose mifepristone in medical management of uterine leiomyoma - an experience from a tertiary care hospital from north India. Indian Journal of Medical Research 137: 1154-62																
Comparison	Mifepristone 25mg/d																
Methods	Patients were randomised to receive either 10mg or 25mg of mifepristone per day for 3 months. They were followed up 3 months after the end of treatment.																
Length of follow up	Treatment duration 3 months. 3 months follow up after treatment.																
Location	India, secondary care																
Outcomes measures and effect size	<p>Fibroid volume (not included in analysis as confidence intervals not reported or calculable)</p> <table> <tr> <th></th><th>Mifepristone 10mg/d</th><th>Mifepristone 25mg/d</th></tr> <tr> <td>Baseline</td><td>mean=147.6 range=1.22 to 1358 n=75</td><td>mean=176.8 range=5.4 to 923 n=75</td></tr> <tr> <td>End of treatment (3 months)</td><td>mean=114.4 range=1.13 to 542 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)</td><td>mean=113.7 range=0.52 to 689 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)</td></tr> <tr> <td>3 months follow up</td><td>mean=138.8 range=1.3 to 670.3 n=75* not reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)</td><td>mean=129.9 range=0.52 to 898 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)</td></tr> </table> <p>*n reported as 75 throughout, but this is inconsistent with number of dropouts for an available case analysis, and no details of an intention to treat analysis with imputation of missing data are given.</p> <p>Endometrial hyperplasia (hyperplasia without atypia)</p> <table> <tr> <th></th><th>Mifepristone 10mg/d</th><th>Mifepristone 25mg/d</th></tr> </table>			Mifepristone 10mg/d	Mifepristone 25mg/d	Baseline	mean=147.6 range=1.22 to 1358 n=75	mean=176.8 range=5.4 to 923 n=75	End of treatment (3 months)	mean=114.4 range=1.13 to 542 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)	mean=113.7 range=0.52 to 689 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)	3 months follow up	mean=138.8 range=1.3 to 670.3 n=75* not reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)	mean=129.9 range=0.52 to 898 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)		Mifepristone 10mg/d	Mifepristone 25mg/d
	Mifepristone 10mg/d	Mifepristone 25mg/d															
Baseline	mean=147.6 range=1.22 to 1358 n=75	mean=176.8 range=5.4 to 923 n=75															
End of treatment (3 months)	mean=114.4 range=1.13 to 542 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)	mean=113.7 range=0.52 to 689 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)															
3 months follow up	mean=138.8 range=1.3 to 670.3 n=75* not reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)	mean=129.9 range=0.52 to 898 n=75* reported as significant reduction (p,0.05) compared with baseline (Wilcoxon rank sum test)															
	Mifepristone 10mg/d	Mifepristone 25mg/d															

Bibliographic reference	Kulshrestha V, Kriplani A, Agarwal N et al. (2013) Low dose mifepristone in medical management of uterine leiomyoma - an experience from a tertiary care hospital from north India. Indian Journal of Medical Research 137: 1154-62		
	Baseline	4/75	7/75
	End of treatment (3 months)	3/75*	4/75*
	*n reported as 75 throughout, but this is inconsistent with number of dropouts for an available case analysis, and no details of an intention to treat analysis with imputation of missing data are given.		
	Endometrial thickness (surrogate for endometrial hyperplasia) (data not used in analysis as 95%CI not reported or calculable)		
		Mifepristone 10mg/d	Mifepristone 25mg/d
	Baseline	median=7.0 95%CI=not reported n=75	median=6.7 95%CI=not reported n=75
	End of treatment (3 months)	median=7.1 95%CI=not reported n=75	median=7.3 95%CI=not reported n=75
	3 months follow up	median=6.0 95%CI=not reported n=75	median=6.3 95%CI=not reported n=75
reported but not extracted: Menstrual blood loss (no measure of variability, such as standard deviation reported or calculable), Dysmenorrhea, Pain, Backache, Dyspareunia, Haemoglobin, Oestradiol, doppler indices			
Source of funding	Indian Council of Medical Research		
Comments	Randomisation: Randomisation was by computer (further details not reported). Allocation concealment: Not reported. Blinding: Not reported (presume unblinded). Other: n reported as 75 throughout, but this is inconsistent with number of dropouts for an available case analysis, and no details of an intention to treat analysis with imputation of missing data are given.		

1 Table 20: Reinsch 1994

Bibliographic reference	Reinsch RC, Murphy AA, Morales AJ et al. (1994) The effects of RU 486 and leuprolide acetate on uterine artery blood flow in the fibroid uterus: a prospective, randomized study. American journal of obstetrics and gynaecology 170: 1623-7													
Study type	Randomised controlled trial													
Aim	To examine the effects of mifepristone and leuprolide acetate on uterine artery blood flow and uterine volume in women with fibroids.													
Patient characteristics	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> - Scheduled to have hysterectomy or myomectomy - No further inclusion criteria reported <p>Exclusion criteria:</p> <ul style="list-style-type: none"> - None reported <p>Baseline characteristics (of intention to treat population)</p> <table border="1"> <thead> <tr> <th></th><th>Mifepristone 25mg/d</th><th>Leuprolide acetate 3.25mg/month</th></tr> </thead> <tbody> <tr> <td>Age (mean,sd)</td><td>Not reported</td><td>Not reported</td></tr> <tr> <td>Race</td><td>Not reported</td><td>Not reported</td></tr> <tr> <td>Fibroid type</td><td>Not reported</td><td>Not reported</td></tr> </tbody> </table> <p>See outcome measures for baseline measures of reported outcomes</p>			Mifepristone 25mg/d	Leuprolide acetate 3.25mg/month	Age (mean,sd)	Not reported	Not reported	Race	Not reported	Not reported	Fibroid type	Not reported	Not reported
	Mifepristone 25mg/d	Leuprolide acetate 3.25mg/month												
Age (mean,sd)	Not reported	Not reported												
Race	Not reported	Not reported												
Fibroid type	Not reported	Not reported												
Number of Patients	<table border="1"> <thead> <tr> <th></th><th>Mifepristone 25mg/d</th><th>Leuprolide acetate 3.25mg/month</th></tr> </thead> <tbody> <tr> <td>N (Randomised)</td><td>8</td><td>6</td></tr> <tr> <td>N (Analysis)</td><td>8</td><td>6</td></tr> <tr> <td>Drop outs</td><td>0</td><td>0</td></tr> </tbody> </table>			Mifepristone 25mg/d	Leuprolide acetate 3.25mg/month	N (Randomised)	8	6	N (Analysis)	8	6	Drop outs	0	0
	Mifepristone 25mg/d	Leuprolide acetate 3.25mg/month												
N (Randomised)	8	6												
N (Analysis)	8	6												
Drop outs	0	0												
Intervention	Mifepristone 25mg/d for 3 months													
Comparison	3.25mg leuprolide acetate intramuscularly once per month for 3 months													
Methods	Participants were randomised to receive mifepristone 25mg/d or 3.25mg leuprolide intramuscularly once per month for 3 months. Treatment began in the early follicular phase of the menstrual cycle. Participants underwent a hysterectomy or myomectomy at the end of the study.													

Bibliographic reference	Reinsch RC, Murphy AA, Morales AJ et al. (1994) The effects of RU 486 and leuprolide acetate on uterine artery blood flow in the fibroid uterus: a prospective, randomized study. American journal of obstetrics and gynaecology 170: 1623-7		
Length of follow up	3 months treatment duration		
Location	USA secondary care setting		
Outcomes measures and effect size	Uterine volume: Assessed by ultrasound (not included in analysis as confidence intervals not reported or calculable)		
		Mifepristone 25mg/d	Leuprolide acetate 3.25mg/month
	Baseline	not reported	Not reported
	End (3 months treatment) Change from baseline (%)	mean=-32% range=-1 to -65 n=8	mean=-54% range=-22 to -84 n=8 *report no significant difference between groups based on t test (p>0.05)
	reported but not extracted: Uterine artery blood flow		
Source of funding	Not reported		
Comments	Randomisation: Allocation was reported as random, but randomisation method not described. Allocation concealment: Not reported Blinding: Not reported, but presume unblinded due to different methods of administration. Other: No baseline data available.		

1 Appendix H: GRADE profiles

2 Table 21: Mifepristone vs Placebo

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone	Placebo	Relative (95% CI)	Absolute	
Quality of life - total score, 0-3 months treatment (Better indicated by higher values)											
2 ¹	randomised trials	serious ^{2,3}	serious ⁴	no serious indirectness	serious ⁵	none	68	57	-	MD 18.4 (-7.05 to 43.86)	VERY LOW
Quality of life - total score, 3-9 months treatment (Better indicated by higher values)											
1 ^{3,6}	randomised trials	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	17	-	MD 31 (14.8 to 47.2)	MODERATE
Quality of life - symptom score, 0-3 months treatment (Better indicated by lower values)											
1 ⁷	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ⁵	none	48	40	-	MD -12.3 (-20.56 to -4.04)	LOW
Menstrual blood loss, 0-3 months treatment (Better indicated by lower values)											
1 ⁶	randomised trials	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	17	-	MD -14 (-19.67 to -8.33)	MODERATE
Menstrual blood loss, 3-6 months treatment (Better indicated by lower values)											
1 ⁶	randomised trials	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	17	-	MD -14.5 (-20.11 to -8.89)	MODERATE
Fibroid volume, 0-3 months treatment [cm3] (Better indicated by lower values)											
3 ⁸	randomised trials	serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁵	none	89	81	-	MD -34.13 (-53.64 to -14.61)	LOW
Uterine volume,0-3 months treatment [cm3] (Better indicated by lower values)											
3 ⁹	randomised trials	serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁵	none	97	83	-	MD -99.84 (-165.56 to -34.11)	LOW
Uterine volume,3-9 months treatment [cm3] (Better indicated by lower values)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone	Placebo	Relative (95% CI)	Absolute	
1 ⁶	randomised trials	serious ³	no serious inconsistency	no serious indirectness	serious ⁵	none	20	17	-	MD -260 (-503.44 to -16.56)	LOW
Uterine hyperplasia, 0-3 months treatment											
1 ¹⁰	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹¹	none	0/8 (0%)	0/11 (0%)	not estimable	not estimable	LOW
Endometrial thickness, 0-3 months treatment [mm] (Better indicated by lower values)											
1 ⁷	randomised trials	serious ²	no serious inconsistency	serious ¹²	serious ¹³	none	58	47	-	MD 1.9 (0.84 to 2.96)	VERY LOW

- 1 1 Esteve 2013, Fiscella 2006
- 2 2 Esteve 2013 had significantly greater number of dropouts in placebo group, and dropouts were not accounted for in analysis.
- 3 3 Fiscella 2006 had poorly matched groups in terms of uterine volume at baseline and unclear reporting of numbers measured at each time point.
- 4 4 Confidence intervals non-overlapping and substantial unexplained heterogeneity (I²=88%)
- 5 5 Confidence intervals incorporate clinically important benefit and no clinically important difference.
- 6 6 Fiscella 2006
- 7 7 Esteve 2013
- 8 8 Bagaria 2009, Engman 2009, Esteve 2013
- 9 9 Bagaria 2009, Esteve 2013, Fiscella 2006
- 10 10 Engman 2009
- 11 11 Effect estimate not calculable (zero events in both arms).
- 12 12 Endometrial thickness is a surrogate outcome for endometrial hyperplasia.
- 13 13 Confidence intervals incorporate clinically important harm and no clinically important difference.

14 **Table 22: Mifepristone 2.5mg vs Mifepristone 5mg**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone 2.5 mg	Mifepristone 5 mg	Relative (95% CI)	Absolute	
Fibroid volume, 0-3 months treatment [cm3] (Better indicated by lower values)											
2 ¹	randomised trials	very serious ²	no serious inconsistency	no serious indirectness	no serious imprecision	none	150	166	-	MD 22.3 (3.35 to 41.25)	LOW
Fibroid volume, 0-3 months follow up [cm3] (Better indicated by lower values)											
1 ³	randomised	serious ⁴	no serious	no serious	serious ⁵	none	98	104	-	MD 35 (-	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone 2.5 mg	Mifepristone 5 mg	Relative (95% CI)	Absolute	
	trials		inconsistency	indirectness						0.38 to 70.38)	
Fibroid volume, 3-9 months follow up [cm3] (Better indicated by lower values)											
1 ³	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	serious ⁵	none	90	100	-	MD 30 (-7.02 to 67.02)	LOW
Uterine volume, 0-3 months treatment [cm3] (Better indicated by lower values)											
2 ¹	randomised trials	very serious ²	serious ⁶	no serious indirectness	no serious imprecision	none	150	166	-	MD 13.78 (46.51 to 74.07)	VERY LOW
Uterine volume, 0-3 months follow up [cm3] (Better indicated by lower values)											
1 ³	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	104	-	MD 39 (-41.97 to 119.97)	MODERATE
Uterine volume, 3-9 months follow up [cm3] (Better indicated by lower values)											
1 ³	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	no serious imprecision	none	90	100	-	MD 6 (-78.2 to 90.24)	MODERATE
Endometrial hyperplasia, 0-3 months treatment											
1 ³	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ⁷	none	0/66 (0%)	0/68 (0%)	not estimable	not estimable	VERY LOW
Endometrial thickness, 0-3 months treatment [mm] (Better indicated by lower values)											
1 ⁸	randomised trials	very serious ²	no serious inconsistency	serious ⁹	serious ¹⁰	none	48	60	-	MD -0.9 (-2.45 to 0.65)	VERY LOW

- 1 1 Carbonell 2012, Carbonell 2013a
- 2 2 Carbonell 2012 had significantly higher dropout rate in 2.5mg group and baseline characteristics (uterine volume) appeared unbalanced across groups. Both studies were unblinded (or presumably unblinded).
- 3 3 Carbonell 2013a
- 4 4 Study unblinded.
- 5 5 Confidence intervals incorporate clinically important benefit of higher dose and no clinically important difference.
- 6 6 Substantial unexplained heterogeneity ($I^2 > 50\%$)
- 7 7 Effect estimate not calculable (zero events in each arm).
- 8 8 Carbonell 2012
- 9 9 Endometrial thickness is a surrogate measure for endometrial hyperplasia.

1 10 Confidence intervals incorporate clinically important harm of higher dose and no clinically important difference.

2 Table 23: Mifepristone 5mg vs Mifepristone 10mg

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone 5mg	Mifepristone 10mg	Relative (95% CI)	Absolute	
Quality of life- total score, 3-9 months treatment (Better indicated by higher values)											
1 ¹	randomised trials	serious ²	no serious inconsistency	no serious indirectness	serious ³	none	31	34	-	MD 3.6 (-7.66 to 14.86)	LOW
Menstrual blood loss (blood loss index), 0-3 months treatment (Better indicated by lower values)											
1 ⁴	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ³	none	20	20	-	MD -3 (-8.47 to 2.47)	LOW
Menstrual blood loss (blood loss index), 3-9 months treatment (Better indicated by lower values)											
1 ⁴	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ⁶	none	20	20	-	MD 5.5 (-1.62 to 12.62)	LOW
Fibroid volume, 0-3 months treatment (Better indicated by lower values)											
1 ⁷	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	50	49	-	MD -26 (-75.05 to 23.05)	MODERATE
Fibroid volume, 3-9 months treatment (Better indicated by lower values)											
2 ⁸	randomised trials	serious ^{2,9}	serious ¹⁰	no serious indirectness	very serious ¹¹	none	105	104	-	MD -4.71 (-63.51 to 54.09)	VERY LOW
Fibroid volume, 9+ months follow up (Better indicated by lower values)											
2 ⁸	randomised trials	serious ^{2,9}	serious inconsistency ¹²	no serious indirectness	very serious ¹¹	none	83	82	-	MD -24.99 (-115.54 to 65.57)	VERY LOW
Uterine volume, 0-3 months treatment (Better indicated by lower values)											
2 ^{4,7}	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	69	-	MD -10.02 (-75.21 to 55.18)	MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone 5mg	Mifepristone 10mg	Relative (95% CI)	Absolute	
Uterine volume, 3-9 months treatment (Better indicated by lower values)											
3 ^{4,8}	randomised trials	serious ^{2,5,9}	no serious inconsistency	no serious indirectness	no serious imprecision	none	125	125	-	MD 21.09 (-5.26 to 47.43)	MODERATE
Uterine volume, 9+ months follow up (Better indicated by lower values)											
2 ⁸	randomised trials	serious ^{2,9}	no serious inconsistency	no serious indirectness	no serious imprecision	none	83	82	-	MD 57.11 (-26.61 to 140.84)	MODERATE
Endometrial hyperplasia, 0-3 months treatment											
1 ⁷	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ¹¹	none	0/50 (0%)	1/49 (2%)	RR 0.33 (0.01 to 7.83)	14 fewer per 1000 (from 20 fewer to 139 more)	LOW
Endometrial hyperplasia, 6-9 months treatment											
2 ^{1,4}	randomised trials	serious ^{2,5}	no serious inconsistency	no serious indirectness	very serious ¹¹	none	4/29 (13.8%)	6/37 (16.2%)	RR 0.83 (0.28 to 2.46)	28 fewer per 1000 (from 117 fewer to 237 more)	VERY LOW
Endometrial hyperplasia, 9+ months treatment											
1 ⁴	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	very serious ¹¹	none	4/16 (25%)	6/20 (30%)	RR 0.83 (0.28 to 2.46)	51 fewer per 1000 (from 216 fewer to 438 more)	VERY LOW
Endometrial thickness, 0-3 months treatment [mm] (Better indicated by lower values)											
1 ¹	randomise	serious ²	no serious	serious ¹³	serious ³	none	31	35	-	MD -3.2	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone 5mg	Mifepristone 10mg	Relative (95% CI)	Absolute	
	d trials		inconsistency							(-5.66 to -0.74)	
Endometrial thickness, 3-9 months treatment [mm] (Better indicated by lower values)											
2 ⁸	randomised trials	serious ^{2,9}	serious ¹²	serious ¹³	serious ³	none	105	105	-	MD -1.82 (-4.14 to 0.51)	VERY LOW
Endometrial thickness, 9 months+ follow up [mm] (Better indicated by lower values)											
1 ¹⁴	randomised trials	serious ⁹	no serious inconsistency	serious ¹³	no serious imprecision	none	74	70	-	MD 0 (-0.69 to 0.69)	LOW

- 1 1 Carbonell 2013b
- 2 2 Carbonell 2013b poorly matched in terms of fibroid and uterine volume at baseline (10mg group larger volume).
- 3 3 Confidence intervals incorporate clinically important harm of higher dose and no clinically important difference.
- 4 4 Eisinger 2003
- 5 5 Eisinger 2003 study was unblinded.
- 6 6 Confidence intervals incorporate clinically important benefit of higher dose and no clinically important difference.
- 7 7 Carbonell 2008
- 8 8 Carbonell 2013b, Esteve 2012
- 9 9 Esteve 2012 was presumably unblinded (no details but assumed from method of allocation).
- 10 10 Confidence intervals are non-overlapping and substantial unexplained heterogeneity (I²>50%)
- 11 11 Confidence intervals incorporate both clinically important benefit and harm of higher dose.
- 12 12 Substantial unexplained heterogeneity (I²>50%)
- 13 13 Endometrial thickness is a surrogate measure for endometrial hyperplasia.
- 14 14 Esteve 2012

15 **Table 24: Mifepristone 10mg vs Mifepristone 25mg**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone 10mg	Mifepristone 25mg	Relative (95% CI)	Absolute	
Endometrial hyperplasia, 0-3 months treatment											
1 ¹	randomised trials	serious ²	no serious inconsistency	no serious indirectness	very serious ³	none	3/75 (4%)	4/75 (5.3%)	RR 0.75 (0.17 to 3.24)	13 fewer per 1000 (from 44 fewer to 119 more)	VERY LOW

- 1 1 Kulshrestha 2013
2 2 Study presumably unblinded (no details of blinding provided). Also, details of number of participants is inconsistent with number of reported dropouts, and no details are provided on how missing data was imputed.
3 3 Confidence intervals incorporate both clinically important benefit and harm of higher dose.

5 Table 25: Ulipristal acetate 5mg vs Placebo

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate 5mg	Placebo	Relative (95% CI)	Absolute	
Menstrual blood loss (pictorial blood loss assessment, change from baseline), 0-3 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	95	48	Median diff -291 (-399 to -194)	-	HIGH
Fibroid volume (% change from baseline), 0-3 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	95	48	Median diff -22.6 (-36.1 to -8.2)	-	MODERATE
Uterine volume (number with 25% reduction), 0-3 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	30/88 (34.1%)	24/85 (28.2%)	RR 1.21 (0.77 to 1.89)	-	MODERATE
Endometrial hyperplasia, 0-3 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	0/83 (0%)	0/41 (0%)	not estimable	not estimable	LOW
Endometrial hyperplasia, 3-9 months follow up											
1 ¹	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ⁵	none	0/63 (0%)	1/31 (3.2%)	RR 0.17 (0.01 to 3.98)	27 fewer per 1000 (from 32 fewer to 96 more)	VERY LOW
Endometrial thickness, 0-3 months treatment [mm] (Better indicated by lower values)											
1 ¹	randomised trials	no serious	no serious inconsistency	serious ⁶	no serious imprecision	none	95	48	-	MD 0.45 (-1.12 to	MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate 5mg	Placebo	Relative (95% CI)	Absolute	
		risk of bias								2.02)	
Endometrial thickness, 0-3 months follow up [mm] (Better indicated by lower values)											
1 ¹	randomised trials	serious ⁷	no serious inconsistency	serious ⁶	serious ⁸	none	49	26	-	MD -0.5 (-2.26 to 1.26)	VERY LOW
Endometrial thickness, 3-9 months follow up [mm] (Better indicated by lower values)											
1 ¹	randomised trials	serious ⁷	no serious inconsistency	serious ⁶	serious ⁸	none	49	26	-	MD -0.32 (-2.33 to 1.69)	VERY LOW
Number undergoing surgical/radiological treatment, 0-3 months treatment											
1 ¹	randomised trials	no serious	no serious inconsistency	no serious	very serious imprecision ⁵	none	41/91 (45.1%)	19/47 (40.4%)	RR 1.11 (0.74 to 0.69)	-	LOW

1 1 Donnez 2012a

2 2 Confidence intervals incorporate clinically important benefit or harm and no clinically important difference. Note that for the purposes of grading imprecision, standard deviations were calculated by the rule of thumb that the inter-quartile range is approximately equal to 1.35 times the standard deviation.

3 3 No effect size estimable (no events in either arm).

4 4 Follow up measure only included participants who had not undergone hysterectomy or endometrial ablation (approximately 2/3 of original sample)

5 5 Confidence intervals incorporate clinically important benefit and harm.

6 6 Endometrial thickness is a surrogate measure of endometrial hyperplasia.

7 7 Follow up measure only included participants who had not undergone hysterectomy, myomectomy or uterine artery embolization (approximately half of original sample).

8 8 Confidence intervals incorporate clinically important benefit and no effect.

10 **Table 26: Ulipristal acetate 5mg vs Leuprolide acetate**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate 5mg	Leuprolide acetate	Relative (95% CI)	Absolute	
Quality of life (UFS-Quoll total score, change from baseline) (Better indicated by higher values)											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	93	93	-	MD 0.5 (-7.42 to 8.42)	HIGH

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate 5mg	Leuprolide acetate	Relative (95% CI)	Absolute	
Menstrual blood loss (pictorial blood loss assessment, change from baseline), 0-3 months											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	93	93	Median diff 6 (-54 to 63)	-	HIGH
Fibroid volume (ratio change from baseline), 0-3 months treatment [cm3]											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	93	93	Ratio re Leuporeline 1.23 (0.99 to 1.52)	-	MODERATE
Uterine volume (ratio change from baseline), 3-9 months treatment [cm3]											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	93	93	Ratio re Leuporelin 1.48 (1.25 to 1.74)	-	HIGH
Endometrial hyperplasia, 0-3 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ³	none	1/94 (1.1%)	0/95 (0%)	RR 3.03 (0.13 to 73.49)	-	LOW
Endometrial hyperplasia, 3-9 months follow up											
1 ¹	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ⁵	none	0/63 (0%)	0/64 (0%)	Not estimable	Not estimable	VERY LOW
Endometrial thickness, 0-3 months treatment [mm] (Better indicated by lower values)											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious ⁶	no serious imprecision	none	97	101	-	MD 4.3 (2.98 to 5.62)	MODERATE
Endometrial thickness, 3-9 months follow up [mm] (Better indicated by lower values)											
1 ¹	randomised trials	serious ⁷	no serious inconsistency	serious ⁶	no serious imprecision	none	73	73	-	MD 0.1 (-1.48 to 1.28)	LOW
Number undergoing surgical/radiological treatment, 0-3 months treatment											
1 ¹	randomised	no	no serious	no serious	serious	none	50/95	52/95	RR 0.96	-	MODERATE

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate 5mg	Leuprolide acetate	Relative (95% CI)	Absolute	
	trials	serious	inconsistency		imprecision ⁸		(52.6%)	(54.7%)	(0.74 to 1.25)		

- 1 1 Donnez 2012b
2 2 Confidence intervals incorporate clinically important benefit of leuproreline acetate and no clinically important difference.
3 3 Confidence intervals incorporate both clinically important harm and benefit.
4 4 Only those no undergoing hysterectomy or endometrial ablation were included. Denominator not reported, but inferred by reviewer.
5 5 Effect estimate not calculable (no events in either arm).
6 6 Endometrial thickness is a surrogate outcome for endometrial hyperplasia.
7 7 Only those not undergoing hysterectomy or myomectomy were included in follow up measures.
8 8 Confidence intervals incorporate clinically important benefit of ulipristal acetate and no clinically important difference.

9 Table 27: Ulipristal acetate 5mg vs Ulipristal acetate 10mg

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate 5mg	Ulipristal acetate 10mg	Relative (95% CI)	Absolute	
Quality of life (UFS-Quoll total score, change from baseline), 0-3 months treatment (Better indicated by higher values)											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	166	163	-	MD 3.6 (-1.08 to 8.28)	HIGH
Quality of life (UFS-Quoll symptom score, change from baseline), 0-3 months treatment (Better indicated by lower values)											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	167	163	-	MD 1 (-5.51 to 3.51)	HIGH
Quality of life (UFS-Quoll total score, change from baseline), 3-9 months treatment (Better indicated by higher values)											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	148	148	-	MD 0.6 (-4.21 to 5.41)	HIGH
Quality of life (UFS-Quoll symptom score, change from baseline), 3-9 months treatment (Better indicated by lower values)											
1 ¹	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	no serious imprecision	none	149	147	-	MD -0.5 (-5.6 to 4.6)	HIGH

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate 5mg	Ulipristal acetate 10mg	Relative (95% CI)	Absolute	
		bias									
Menstrual blood loss (pictorial blood loss assessment, change from baseline) 0-3 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	167	151		Median diff -13 (-54 to 28)	HIGH
Menstrual blood loss (pictorial blood loss assessment, change from baseline) 3-9 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	152	146		Median diff -28 (-65 to 6)	HIGH
Fibroid volume - number with 25% reduction from baseline, 0-3 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness ⁴	no serious imprecision	none	129/207 (62.3%)	137/206 (66.5%)	RR 0.94 (0.81 to 1.08)	40 fewer per 1000 (from 126 fewer to 53 more)	MODERATE
Fibroid volume - number with 25% reduction from baseline, 3-9 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness ⁴	no serious imprecision	none	139/188 (73.9%)	152/192 (79.2%)	RR 0.93 (0.84 to 1.04)	55 fewer per 1000 (from 127 fewer to 32 more)	MODERATE
Uterine volume - number with 25% reduction from baseline, 0-3 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness ⁴	very serious ²	none	63/214 (29.4%)	66/211 (31.3%)	RR 0.94 (0.71 to 1.26)	19 fewer per 1000 (from 91 fewer to 81 more)	VERY LOW
Uterine volume - number with 25% reduction from baseline, 3-9 months treatment											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness ⁴	serious imprecision ⁵	none	90/194 (46.4%)	90/196 (45.9%)	RR 1.01 (0.82 to 1.25)	5 more per 1000 (from 83 fewer to 115 more)	LOW
Endometrial hyperplasia, 0-3 months treatment											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ulipristal acetate 5mg	Ulipristal acetate 10mg	Relative (95% CI)	Absolute	
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ²	none	1/178 (0.56%)	2/182 (1.1%)	RR 0.51 (0.05 to 5.59)	5 fewer per 1000 (from 10 fewer to 50 more)	LOW
Endometrial thickness, 0-3 months treatment [mm] (Better indicated by lower values)											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	none	214	207	-	MD -0.7 (-1.57 to 0.17)	MODERATE
Endometrial thickness, 3-9 months treatment [mm] (Better indicated by lower values)											
1 ¹	randomised trials	no serious risk of bias	no serious inconsistency	serious ³	no serious imprecision	none	192	193	-	MD 0.4 (0.41 to 1.21)	MODERATE

1 1 Donnez 2015

2 2 Confidence intervals incorporate both clinically important benefit and harm of higher dose.

3 3 Endometrial thickness is an indirect measure of endometrial hyperplasia

4 4 Number with 25% reduction from baseline is an indirect measure of volume. Topic experts advised that this measure was less clinically useful than a direct measure of volume reduction.

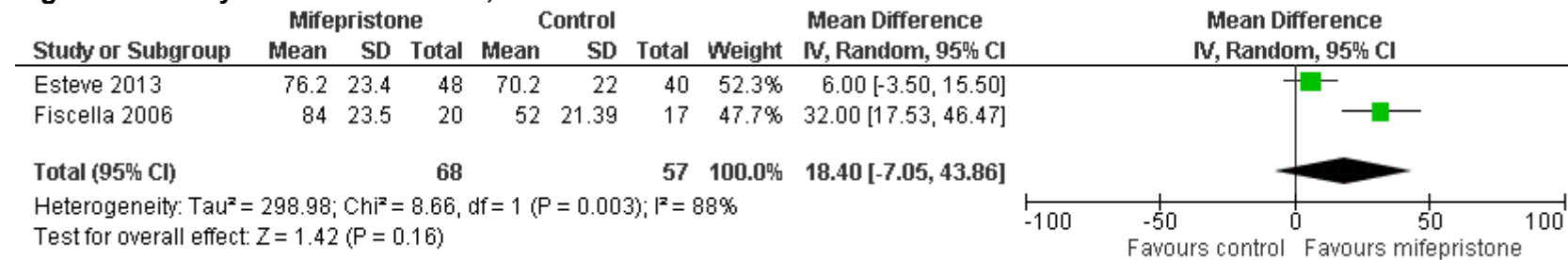
6 5 Confidence intervals incorporate no clinically important difference and clinically important benefit of higher dose.

7

1 Appendix I: Forest plots

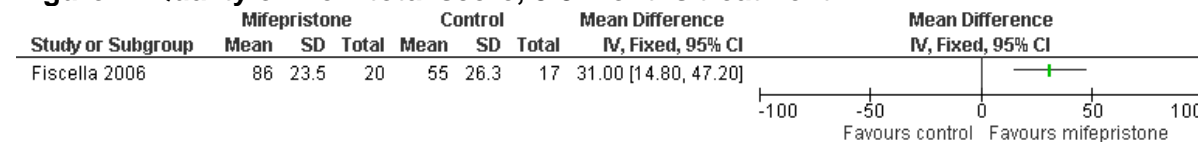
I.1.2 Mifepristone vs Placebo

Figure 3: Quality of life – total score, 0-3 months treatment



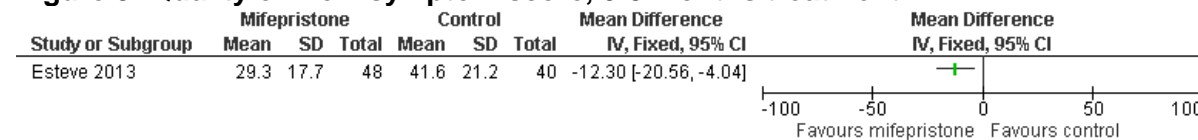
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Figure 4: Quality of life – total score, 3-9 months treatment



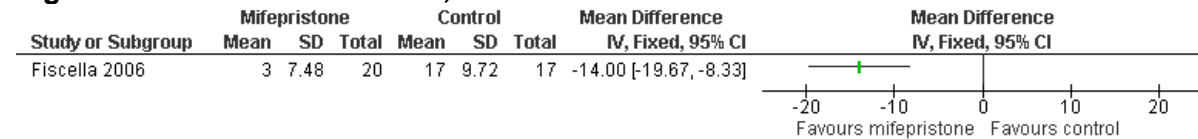
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Figure 5: Quality of life – symptom score, 0-3 months treatment



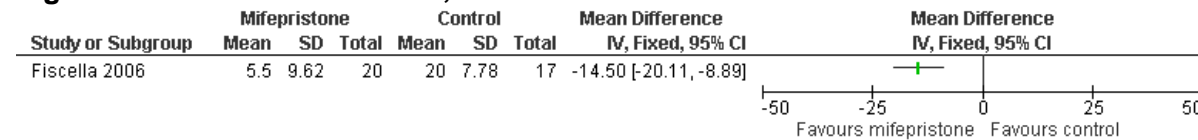
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Figure 6: Menstrual blood loss, 0-3 months treatment



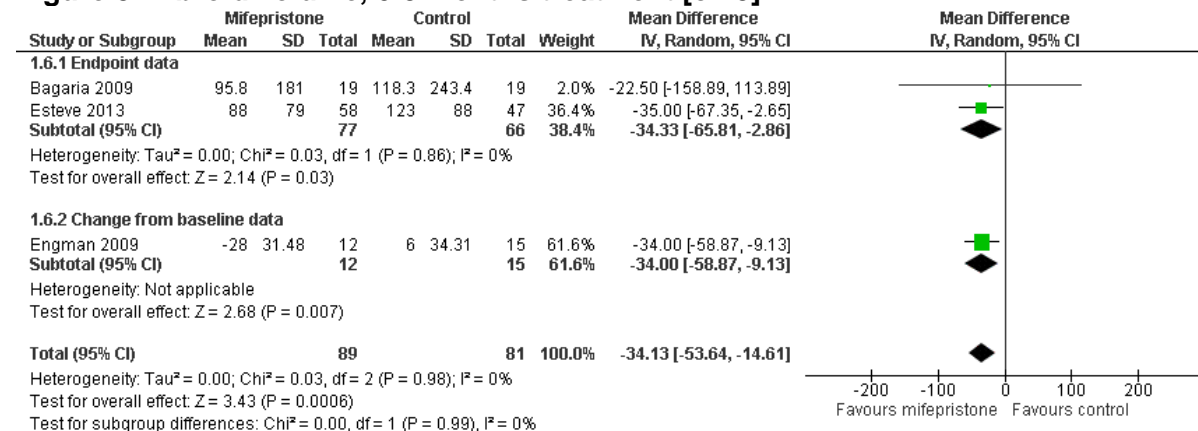
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Figure 7: Menstrual blood loss, 3-9 months treatment



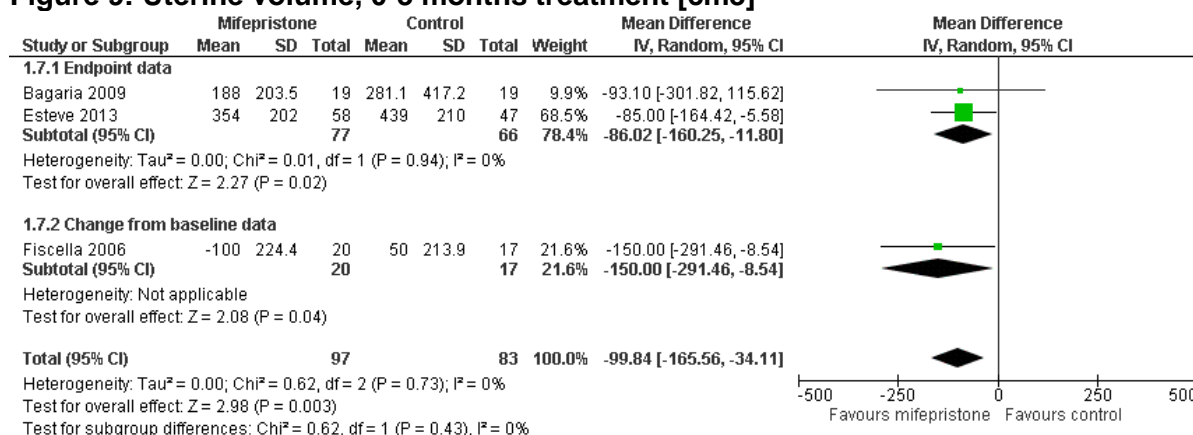
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Figure 8: Fibroid volume, 0-3 months treatment [cm3]



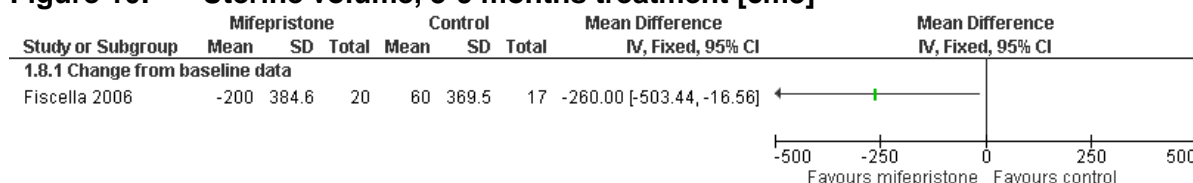
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Figure 9: Uterine volume, 0-3 months treatment [cm3]



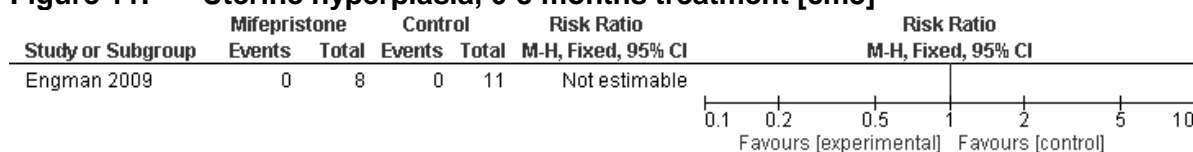
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Figure 10: Uterine volume, 3-9 months treatment [cm3]



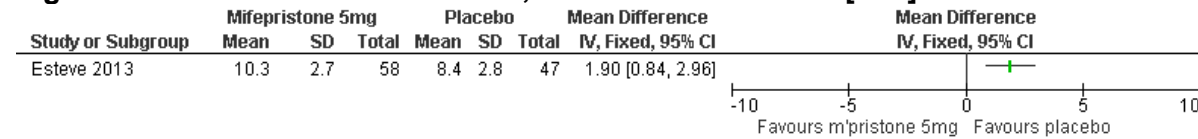
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Figure 11: Uterine hyperplasia, 0-3 months treatment [cm3]



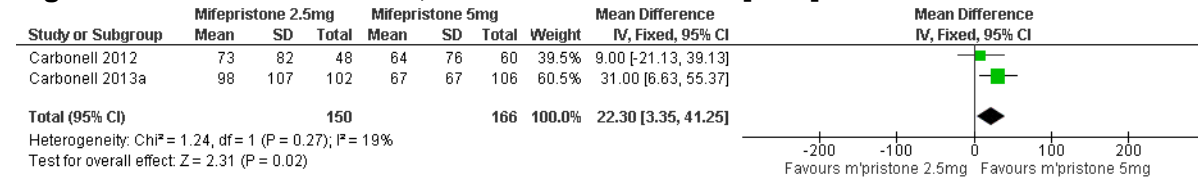
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Figure 12: Endometrial thickness, 0-3 months treatment [mm]



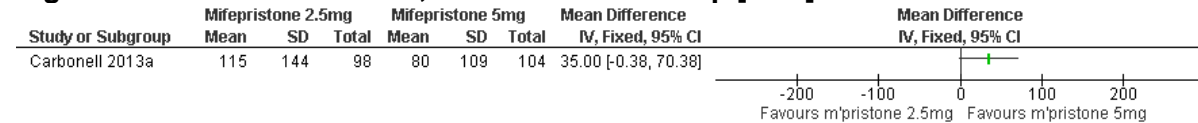
I.2.1 Mifepristone 2.5mg vs Mifepristone 5mg

Figure 13: Fibroid volume, 0-3 months treatment [cm3]



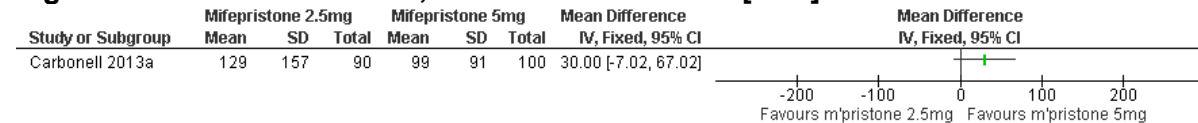
2

Figure 14: Fibroid volume, 0-3 months follow up [cm3]



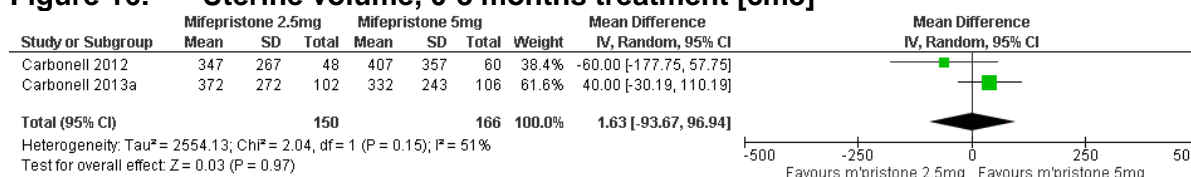
3

Figure 15: Fibroid volume, 3-9 months treatment [cm3]



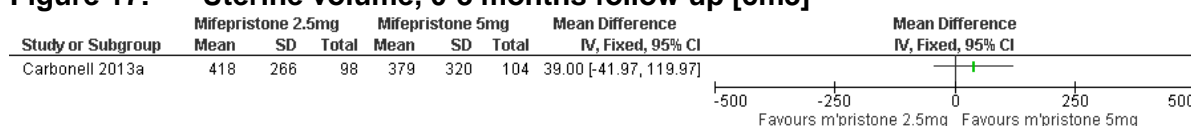
4

Figure 16: Uterine volume, 0-3 months treatment [cm3]



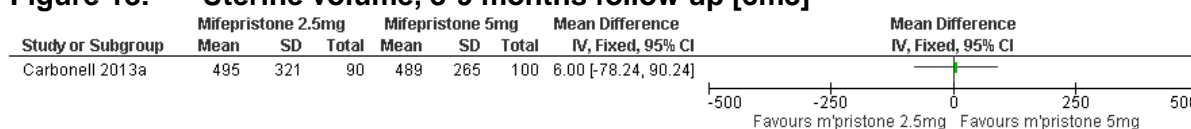
1

Figure 17: Uterine volume, 0-3 months follow up [cm3]



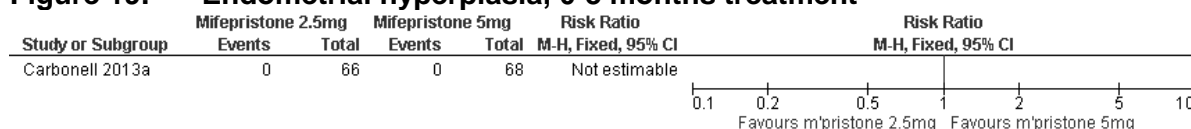
2

Figure 18: Uterine volume, 3-9 months follow up [cm3]



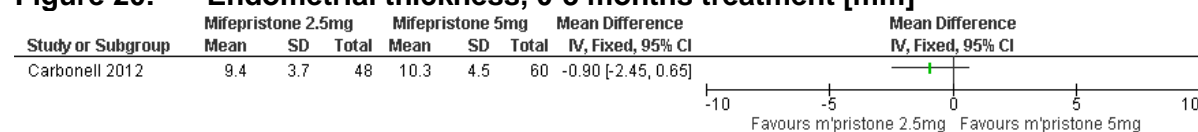
3

Figure 19: Endometrial hyperplasia, 0-3 months treatment



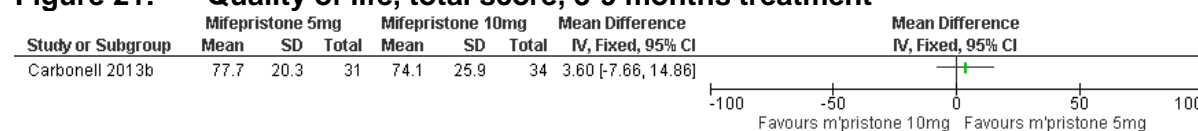
4

Figure 20: Endometrial thickness, 0-3 months treatment [mm]



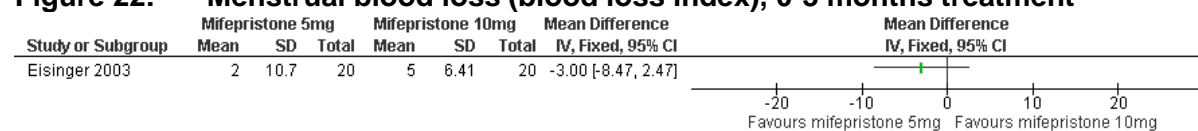
I.3₁ Mifepristone 5mg vs Mifepristone 10mg

Figure 21: Quality of life, total score, 3-9 months treatment



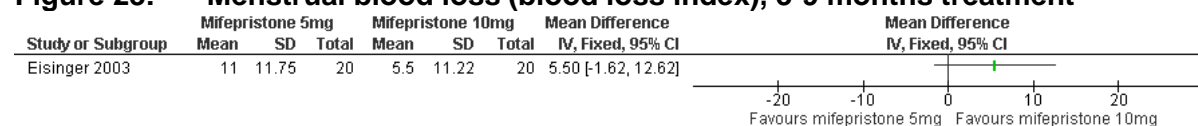
2

Figure 22: Menstrual blood loss (blood loss index), 0-3 months treatment



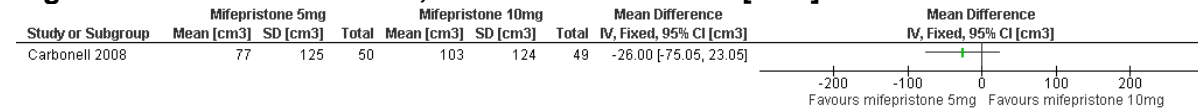
3

Figure 23: Menstrual blood loss (blood loss index), 3-9 months treatment



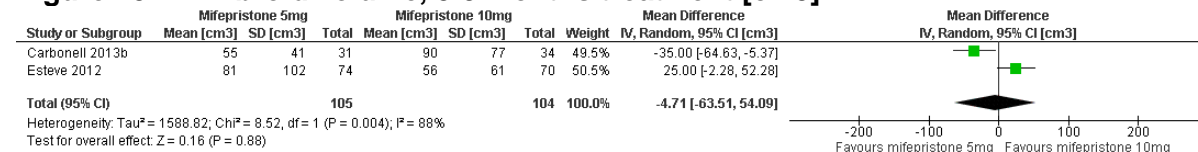
4

Figure 24: Fibroid volume, 0-3 months treatment [cm3]



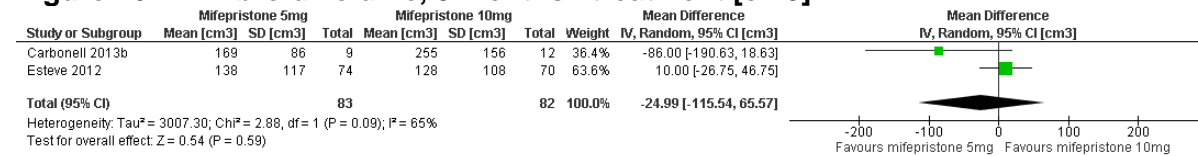
1

Figure 25: Fibroid volume, 3-9 months treatment [cm3]



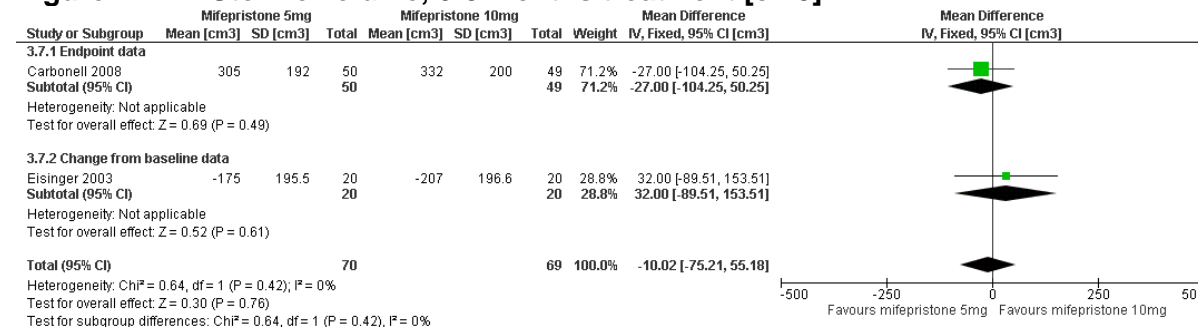
2

Figure 26: Fibroid volume, 9 months+ treatment [cm3]



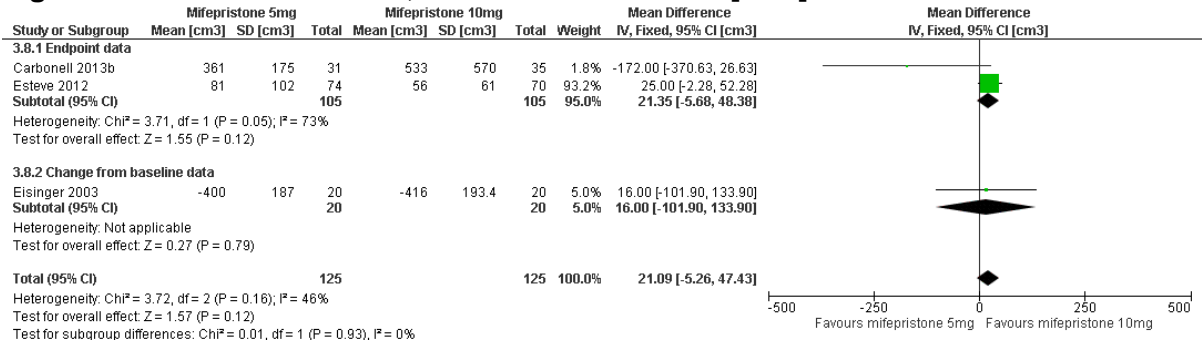
3

Figure 27: Uterine volume, 0-3 months treatment [cm3]



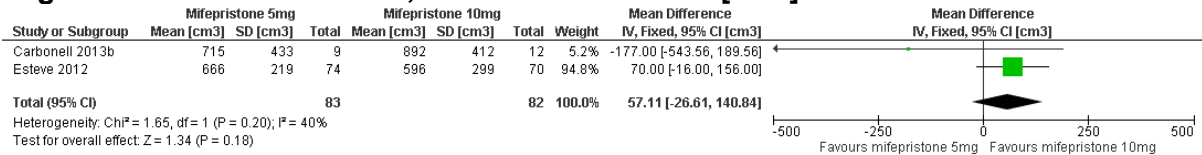
1

Figure 28: Uterine volume, 3-9 months treatment [cm3]



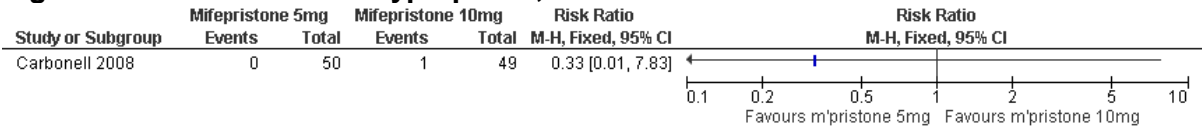
2

Figure 29: Uterine volume, 9 months+ treatment [cm3]



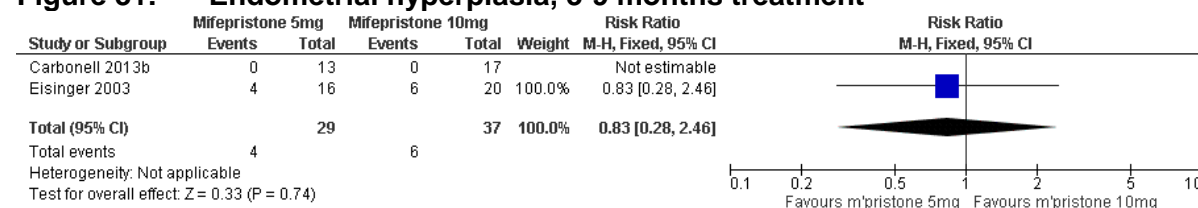
3

Figure 30: Endometrial hyperplasia, 0-3 months treatment



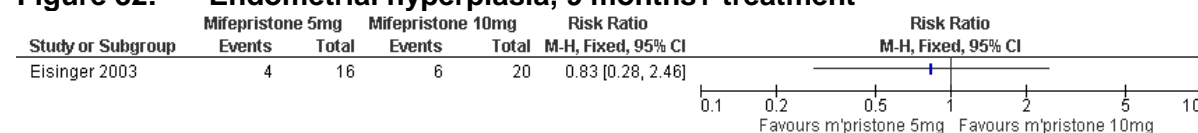
4

Figure 31: Endometrial hyperplasia, 3-9 months treatment



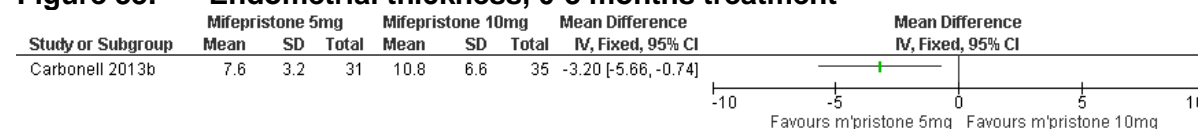
1

Figure 32: Endometrial hyperplasia, 9 months+ treatment



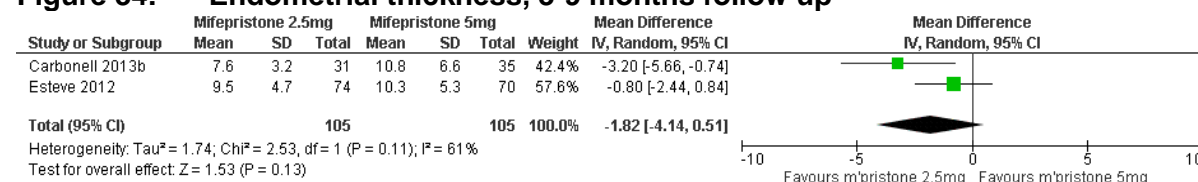
2

Figure 33: Endometrial thickness, 0-3 months treatment



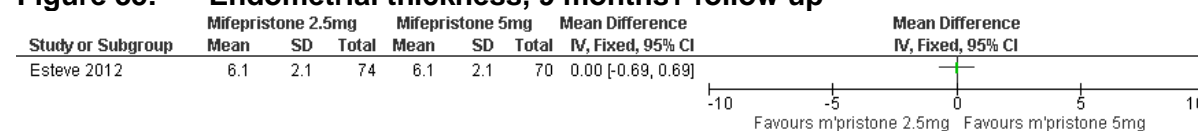
3

Figure 34: Endometrial thickness, 3-9 months follow up



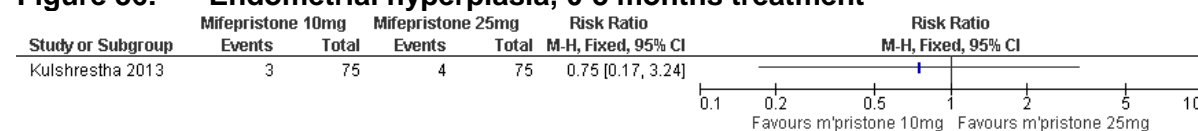
1

Figure 35: Endometrial thickness, 9 months+ follow up



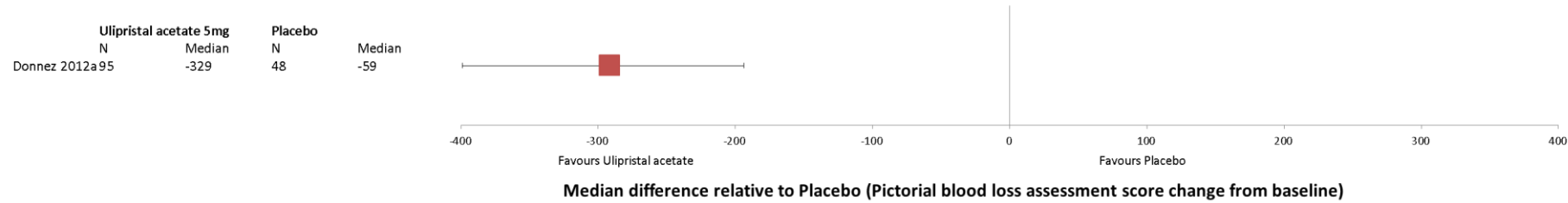
I.4.2 Mifepristone 10mg vs Mifepristone 25mg

Figure 36: Endometrial hyperplasia, 0-3 months treatment



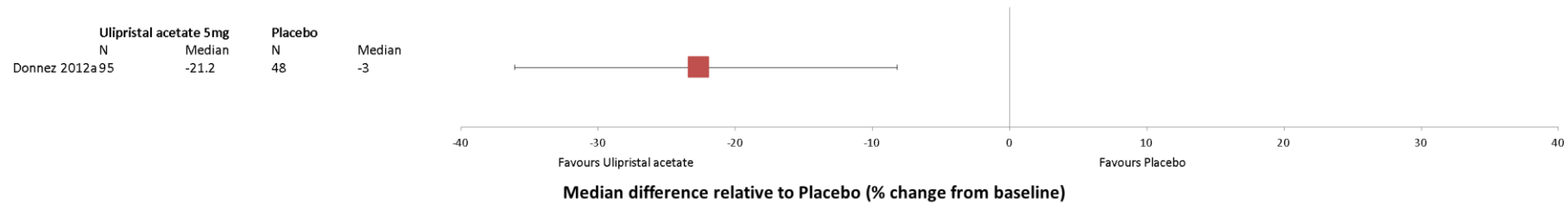
I.5₁ Ulipristal acetate 5mg vs Placebo

Figure 37: Menstrual blood loss (pictorial blood loss assessment, change from baseline), 0-3 months treatment



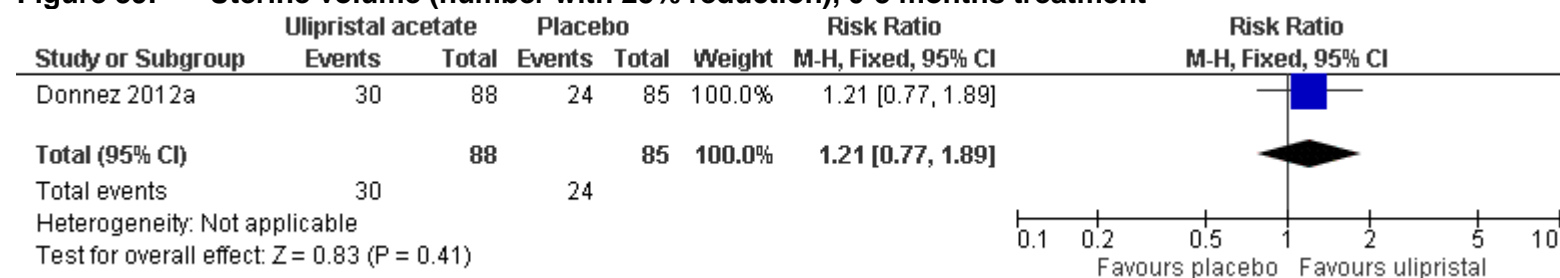
2

Figure 38: Fibroid volume (%change from baseline), 0-3 months treatment



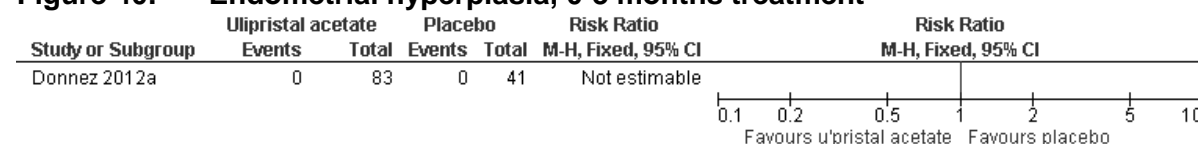
3

Figure 39: Uterine volume (number with 25% reduction), 0-3 months treatment



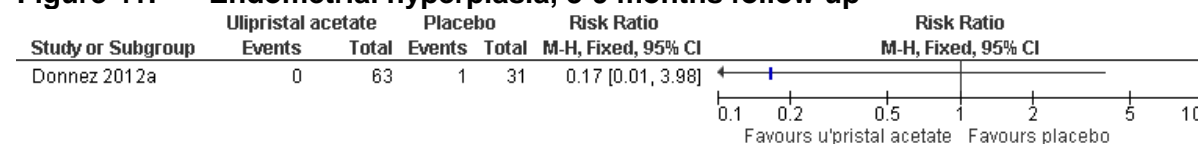
1

Figure 40: Endometrial hyperplasia, 0-3 months treatment



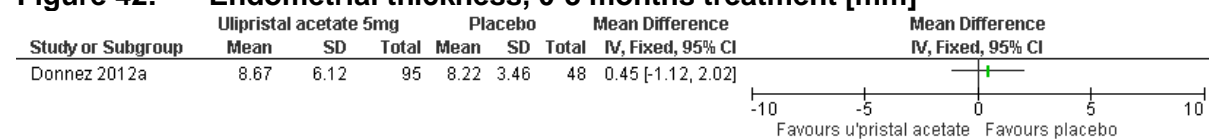
2

Figure 41: Endometrial hyperplasia, 3-9 months follow up



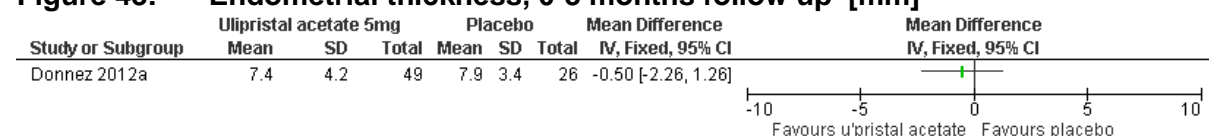
3

Figure 42: Endometrial thickness, 0-3 months treatment [mm]



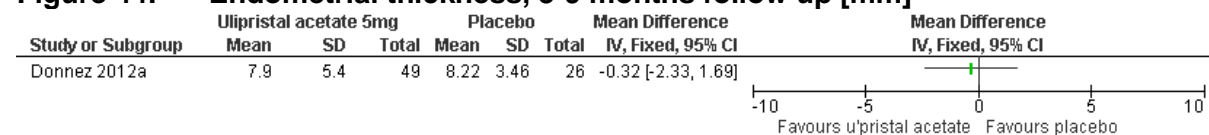
1

Figure 43: Endometrial thickness, 0-3 months follow up [mm]



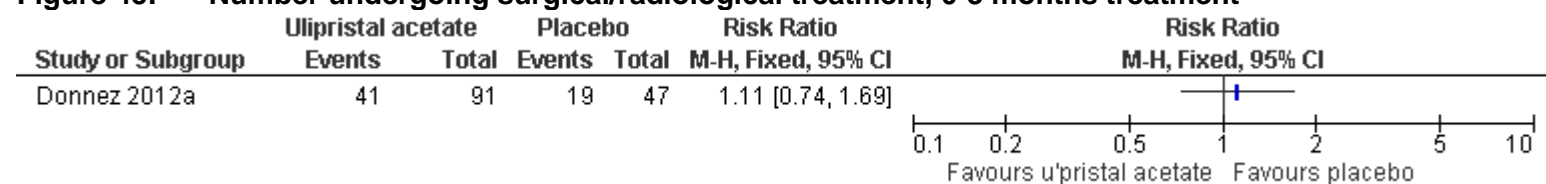
2

Figure 44: Endometrial thickness, 3-9 months follow up [mm]



3

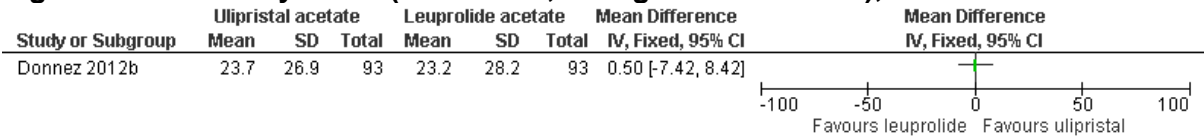
Figure 45: Number undergoing surgical/radiological treatment, 0-3 months treatment



1

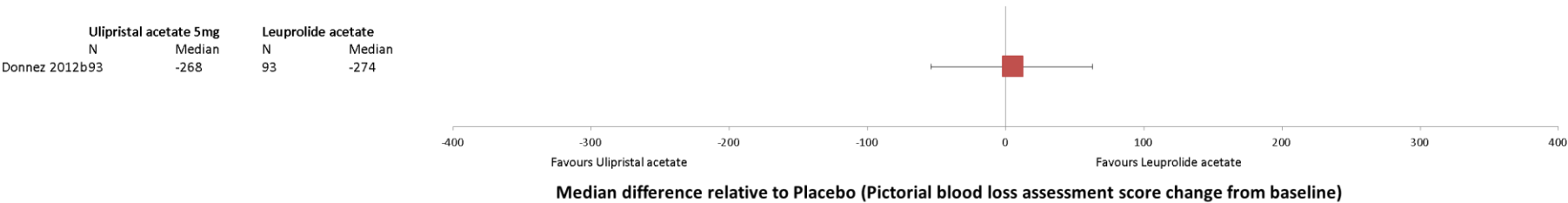
I.62 Ulipristal acetate 5mg vs Leuprolide acetate

Figure 46: Quality of life (total score, change from baseline), 0-3 months treatment



3

Figure 47: Menstrual blood loss (pictorial blood loss assessment, change from baseline), 0-3 months treatment



4

Figure 48: Fibroid volume, (ratio relative to baseline), 0-3 months treatment



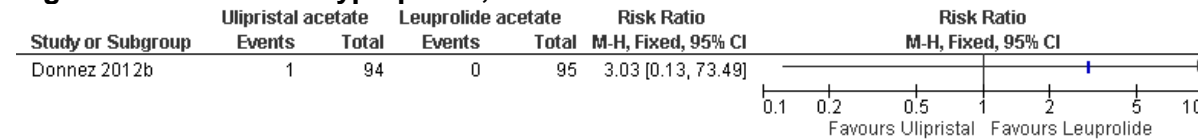
1

Figure 49: Uterine volume, (ratio relative to baseline), 0-3 months treatment



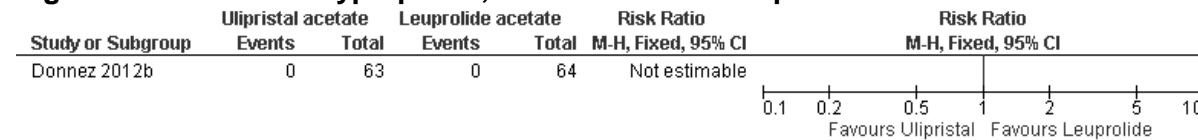
2

Figure 50: Uterine hyperplasia, 0-3 months treatment



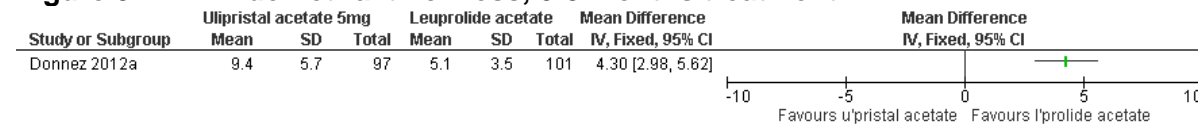
1

Figure 51: Uterine hyperplasia, 3-9 months follow up



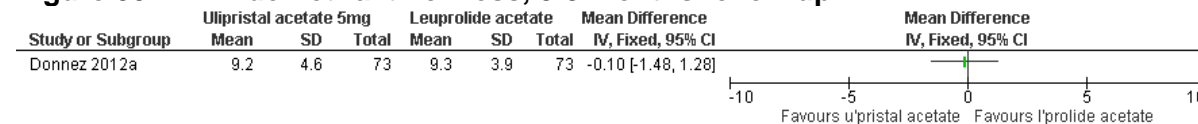
2

Figure 52: Endometrial thickness, 0-3 months treatment



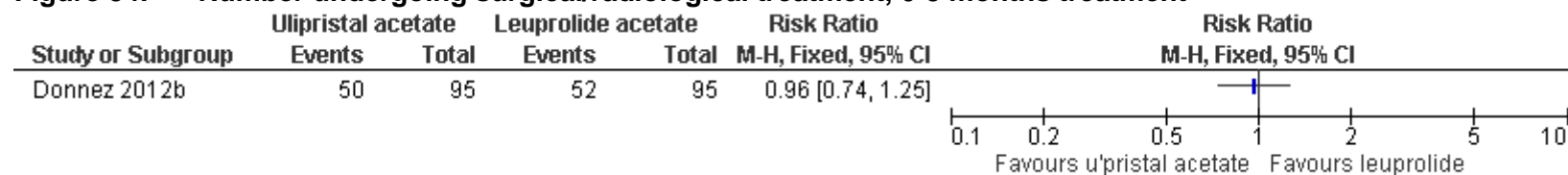
3

Figure 53: Endometrial thickness, 3-9 months follow up



1

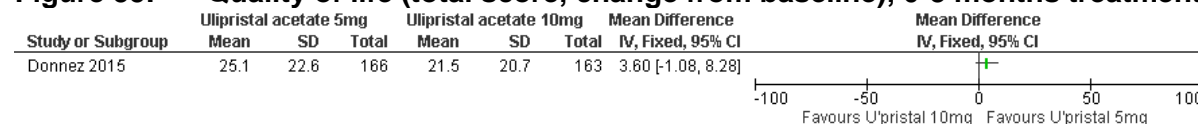
Figure 54: Number undergoing surgical/radiological treatment, 0-3 months treatment



2

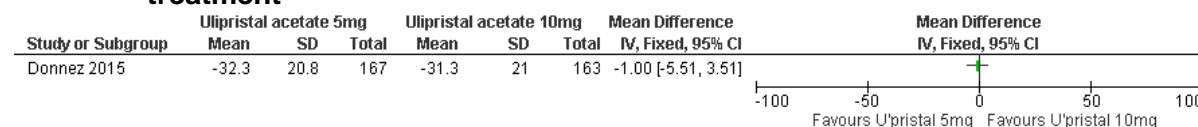
I.7.3 Ulipristal acetate 5mg vs Ulipristal acetate 10mg

Figure 55: Quality of life (total score, change from baseline), 0-3 months treatment



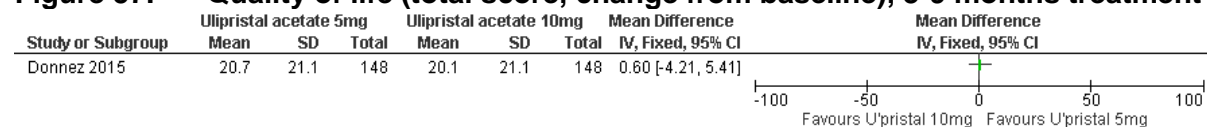
4

Figure 56: Quality of life (symptom score, change from baseline), 0-3 months treatment



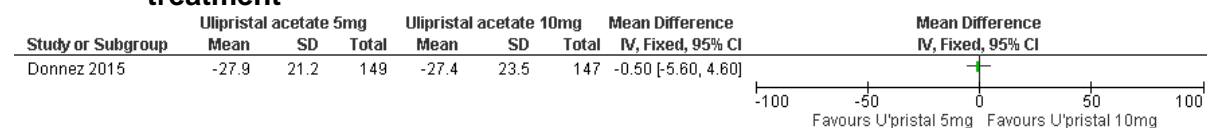
5

Figure 57: Quality of life (total score, change from baseline), 3-9 months treatment



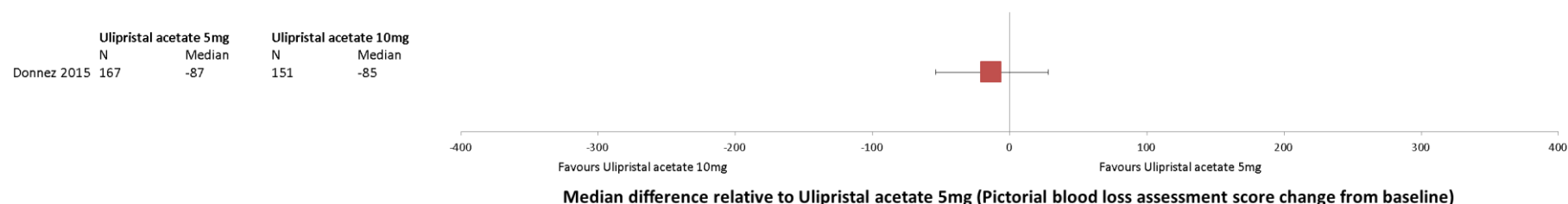
1

Figure 58: Quality of life (symptom score, change from baseline), 3-9 months treatment



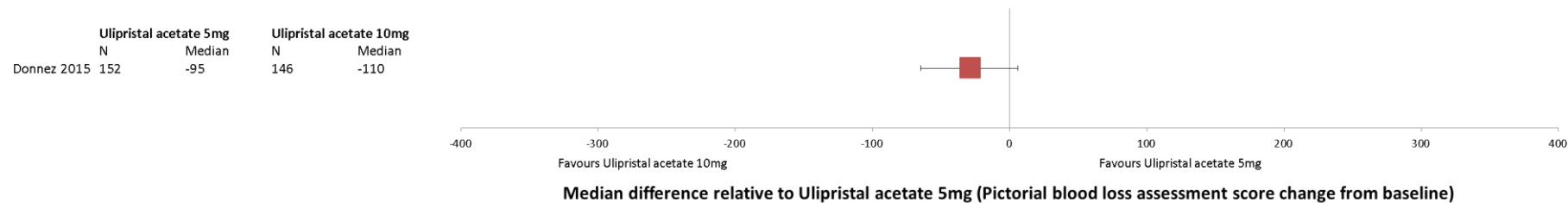
2

Figure 59: Menstrual blood loss (pictorial blood loss assessment, change from baseline), 0-3 months



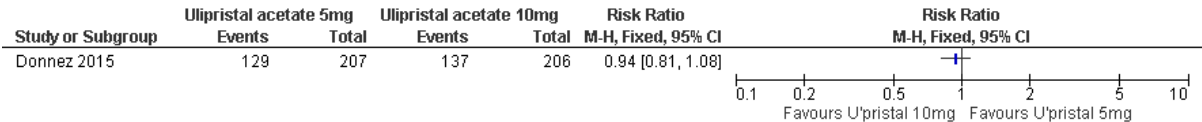
3

Figure 60: Menstrual blood loss (pictorial blood loss assessment, change from baseline), 3-9 months



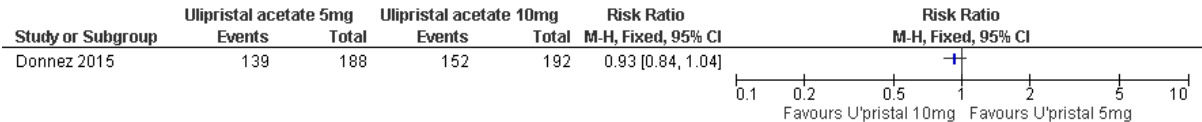
1

Figure 61: Fibroid volume (number with 25% reduction from baseline), 0-3 months treatment



2

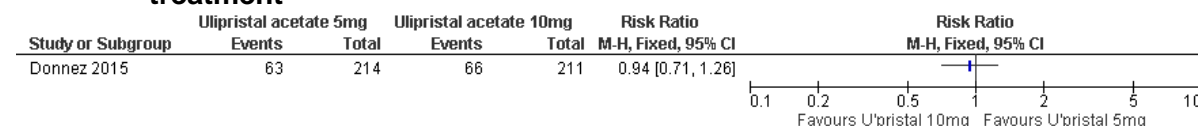
Figure 62: Fibroid volume (number with 25% reduction from baseline), 3-9 months treatment



3

4

Figure 63: Uterine volume (number with 25% reduction from baseline), 0-3 months treatment



1

Figure 64: Uterine volume (number with 25% reduction from baseline), 3-9 months treatment

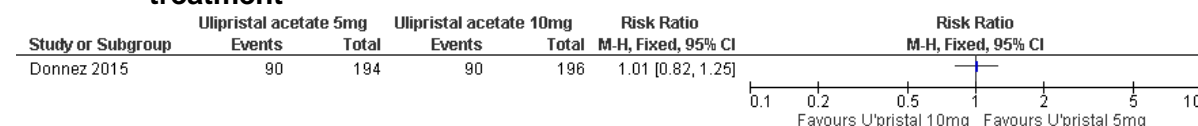
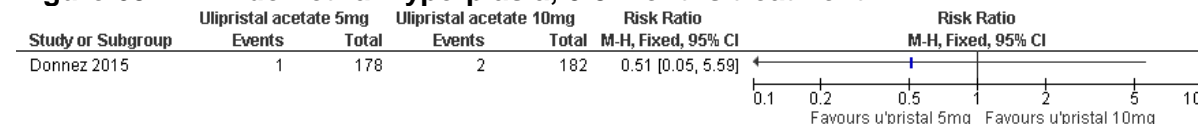
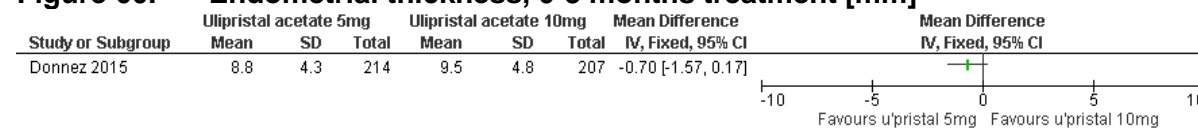


Figure 65: Endometrial hyperplasia, 0-3 months treatment



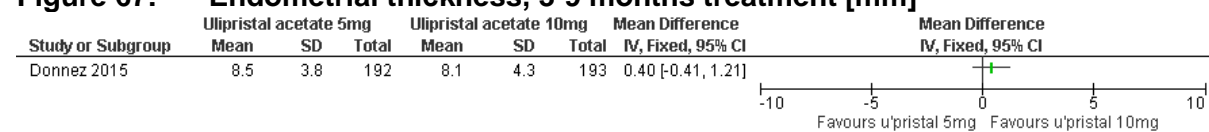
2

Figure 66: Endometrial thickness, 0-3 months treatment [mm]



3

Figure 67: Endometrial thickness, 3-9 months treatment [mm]



1 Appendix J: Economic search strategy

2 Databases that were searched, together with the number of articles retrieved from each
3 database are shown in Table 28. The search strategy is shown in Table 29. The same
4 strategy was translated for the other databases listed.

5 **Table 28: Economic search summary**

Economics	Date searched	Version/files	No. retrieved
MEDLINE (Ovid)	22/09/2015	1946 to September Week 2 2015	52
MEDLINE in Process (Ovid)	22/09/2015	In-Process & Other Non-Indexed Citations <September 18, 2015>	12
Embase (Ovid)	22/09/2015	1974 to 2015 Week 38	117
NHS Economic Evaluation Database (NHS EED) (legacy database)	22/09/2015	Issue 2 of 4, April 2015	150
Health Technology Assessment (HTA Database)	22/09/2015	Issue 3 of 4, July 2015	4

6 **Table 29: Economic search strategy**

Database: Medline
Strategy used:
Database: Ovid MEDLINE(R) <1946 to September Week 2 2015>
Search Strategy:

1 exp Leiomyoma/ (17894)
2 Uterine Neoplasms/ (35946)
3 (leiomyoma* or leimyoma*).tw. (10612)
4 leyomyoma*.tw. (5)
5 (angioleiomyoma* or angiomyoma* or elastomyofibroma* or h?emangioleiomyoma* or h?emangiomyoma* or myofibroma* or myofibromatosis or leiomyoblastoma*).tw. (1304)
6 fibroid*.tw. (4030)
7 fibromyoma*.tw. (624)
8 fibroma*.tw. (9478)
9 myoma*.tw. (4537)
10 (smooth adj4 muscle adj4 (tumour* or tumor*)).tw. (1962)
11 Menorrhagia/ (3725)
12 (menorrhag* or hypermenorrh*).tw. (2846)
13 ((menstru* or period*) adj4 (bleed* or blood* or flow* or loss)).tw. (19385)
14 (dysfunctional adj4 uterine adj4 bleed*).tw. (780)
15 (dysfunctional adj4 uterine adj4 blood*).tw. (5)
16 or/1-15 (80836)
17 Receptors, Progesterone/ (16562)
18 ((progestin* or progesterone*) adj4 receptor*).tw. (18890)
19 (Ulipristal* or uliprisnil*).tw. (133)
20 (esmya or ella or ellaone or ella one).tw. (196)
21 Mifepristone/ (5476)
22 (mifepriston* or mifegyne or korlym or mifeprex).tw. (2746)

Database: Medline

- 23 Norpregnadienes/ (493)
- 24 (Norpregnadiene* or norpregnane* or norpregnatriene* or norpregnene* or pregnadiene* or pregnadienediol* or pregnane* or pregnatriene* or pregnenedione* or pregnene*).tw. (4744)
- 25 or/17-24 (33951)
- 26 16 and 25 (1305)
- 27 animals/ not humans/ (4017726)
- 28 26 not 27 (1244)
- 29 limit 28 to english language (1029)
- 30 Economics/ (26916)
- 31 exp "Costs and Cost Analysis"/ (193551)
- 32 Economics, Dental/ (1885)
- 33 exp Economics, Hospital/ (20760)
- 34 exp Economics, Medical/ (13952)
- 35 Economics, Nursing/ (3939)
- 36 Economics, Pharmaceutical/ (2630)
- 37 Budgets/ (10182)
- 38 exp Models, Economic/ (11098)
- 39 Markov Chains/ (10893)
- 40 Monte Carlo Method/ (21842)
- 41 Decision Trees/ (9367)
- 42 econom\$.tw. (168501)
- 43 cba.tw. (8963)
- 44 cea.tw. (17078)
- 45 cua.tw. (822)
- 46 markov\$.tw. (12775)
- 47 (monte adj carlo).tw. (22549)
- 48 (decision adj3 (tree\$ or analys\$)).tw. (9090)
- 49 (cost or costs or costing\$ or costly or costed).tw. (331008)
- 50 (price\$ or pricing\$).tw. (24748)
- 51 budget\$.tw. (18293)
- 52 expenditure\$.tw. (37453)
- 53 (value adj3 (money or monetary)).tw. (1436)
- 54 (pharmacoeconomic\$ or (pharmaco adj economic\$)).tw. (2959)
- 55 or/30-54 (700143)
- 56 "Quality of Life"/ (131403)
- 57 quality of life.tw. (152464)
- 58 "Value of Life"/ (5509)
- 59 Quality-Adjusted Life Years/ (7993)
- 60 quality adjusted life.tw. (6743)
- 61 (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (5506)
- 62 disability adjusted life.tw. (1400)
- 63 daly\$.tw. (1357)
- 64 Health Status Indicators/ (21060)
- 65 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (16630)
- 66 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1048)
- 67 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2981)
- 68 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (21)
- 69 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or

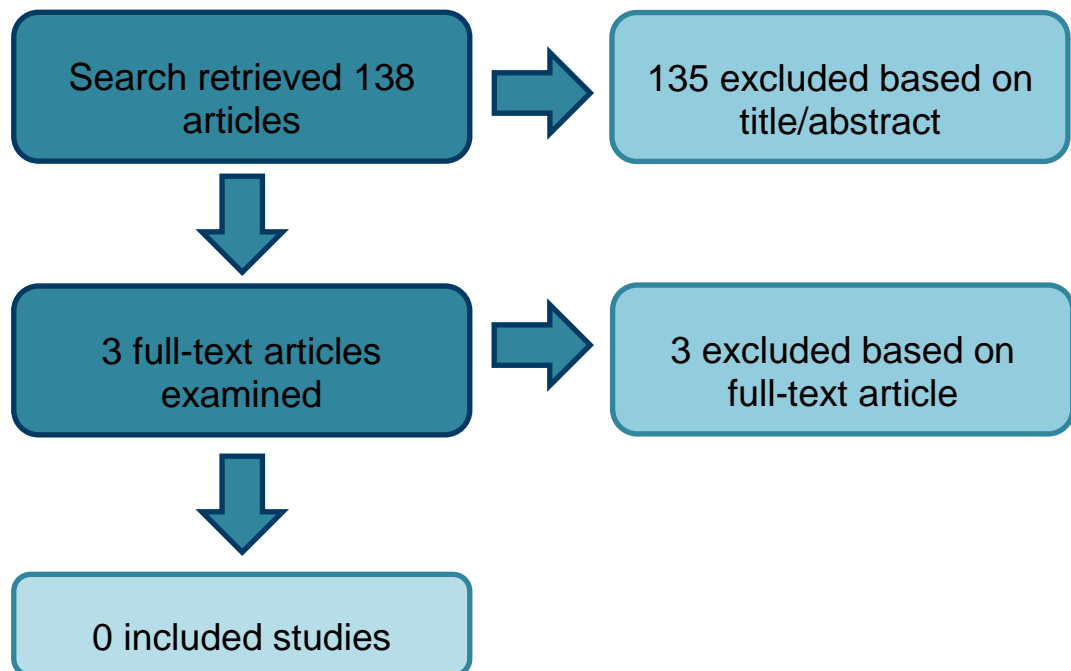
Database: Medline

short form twenty).tw. (341)
70 (euroqol or euro qol or eq5d or eq 5d).tw. (4478)
71 (qol or hql or hqol or hrqol).tw. (27447)
72 (hye or hyes).tw. (54)
73 health\$ year\$ equivalent\$.tw. (38)
74 utilit\$.tw. (122025)
75 (hui or hui1 or hui2 or hui3).tw. (927)
76 disutili\$.tw. (237)
77 rosser.tw. (71)
78 quality of wellbeing.tw. (5)
79 quality of well-being.tw. (348)
80 qwb.tw. (178)
81 willingness to pay.tw. (2497)
82 standard gamble\$.tw. (693)
83 time trade off.tw. (798)
84 time tradeoff.tw. (219)
85 tto.tw. (640)
86 or/56-85 (347837)
87 55 or 86 (1000590)
88 29 and 87 (52)

1 Appendix K: Economic review flowchart

2

3



1 Appendix L: Excluded economic studies

2 The excluded economic studies and reasons for their exclusion are listed in Table 30.

3 **Table 30: Excluded economic studies**

Study	Reason for Exclusion
CADTH, Pharmacoeconomic review report. Ulipristal Acetate (Fibristal - Actavis Specialty Pharmaceuticals Co.) indication: uterine fibroids (Structured abstract), Health Technology Assessment Database, -, 2014	Not applicable. No treatment not included as a comparator and Canadian costs used. This appears to be CADTH's assessment of Tsoi et al 2015 prior to the latter article being published.
Nagy,B., Timar,G., Jozwiak-Hagymasy,J., Kovacs,G., Meresz,G., Vamossy,I., Agh,T., Laszlo,A., Voko,Z., Kalo,Z., 20141217, The cost-effectiveness of ulipristal acetate tablets in treating patients with moderate to severe symptoms of uterine fibroids, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 175, 75-81, 2014	Not applicable. GNRH not included as a comparator and Hungarian costs used.
Tsoi,B., Blackhouse,G., Ferrazzi,S., Reade,C.J., Chen,I., Goeree,R., 20150506, Incorporating ulipristal acetate in the care of symptomatic uterine fibroids: a Canadian cost-utility analysis of pharmacotherapy management, Clinicoeconomics & Outcomes Research, 7, 213-225, 2015	Not applicable. No treatment not included as a comparator and Canadian costs used.

4

Appendix M: Cost-utility analysis of ulipristal acetate vs no treatment for the treatment of fibroids 3 cm or more in diameter

M.1 Introduction

An economic model was developed to investigate the cost utility of ulipristal acetate compared with no treatment for women with heavy menstrual bleeding (HMB) and fibroids 3 cm or more in diameter who are not currently considering treatment with surgical or radiological procedures.

This analysis was undertaken because no relevant economic studies were found from the economic literature review that could guide the Committee's decision. It is necessary to determine the cost effectiveness of ulipristal acetate as a treatment for heavy menstrual bleeding due to the potential resource impact arising from cost of the medicine, need for monitoring for endometrial thickening and the prevalence of women with HMB and fibroids. The original model developed in 2007 investigated the cost utility of pharmaceutical treatments for uncomplicated HMB, i.e. in patients with small (<3cm) fibroids. Given the focus of this update was women with fibroids of 3cm or more, it was inappropriate to use any of the long term modelling done for the previous guideline.

M.2 Overview

Population

The population was adult women of reproductive age with heavy menstrual bleeding and fibroids 3 cm or more in diameter who are not currently considering treatment with surgical or radiological procedures.

Interventions

The following interventions were selected for comparison in the economic model:

- Ulipristal acetate 5 mg/day
- No treatment

Ulipristal acetate 10 mg/day was not included as a treatment alternative because the evidence in the clinical review suggested it was no more effective than 5 mg/day but it costs twice as much. It also does not have a UK marketing authorisation whereas the 5mg preparation does. Mifepristone does not have a UK marketing authorisation for the treatment of uterine fibroids. Leuprorelin acetate has a marketing authorisation for pre-surgical treatment of fibroids to reduce their size and associated bleeding. Ulipristal acetate has a marketing authorisation for both: pre-surgical and longer-term intermittent treatment of fibroids not related to preoperative management. It follows that both mifepristone and leuprorelin acetate are unlicensed for the specified population of women not currently considering treatment with surgical or radiological procedures. Mifepristone or leuprorelin acetate can only be recommended above licensed alternatives (ulipristal acetate) if there is good evidence of superior clinical effectiveness. Based on the current review, the Committee considered that this criterion was not met, and decided

1 not to include mifepristone or leuprorelin acetate in this economic model. Also, it appears that
2 mifepristone is only available in 200 mg tablets in the UK. Given that the studies included in the
3 clinical review used doses ranging from 2.5 mg to 25 mg, mifepristone appears to be
4 unavailable in clinical practice in the UK for this indication, or would be relatively expensive for
5 compounding pharmacists to prepare non-standard doses
6 Uterine artery embolization, myomectomy and hysterectomy have not been included as
7 treatment alternatives because of the population specified above – women not currently
8 considering surgical or radiological procedures. Furthermore, very sparse evidence on surgery
9 in patients receiving ulipristal acetate (1 recorded incident in 1 study) was identified during the
10 clinical review.
11 Also levonorgestrel-releasing intrauterine system, tranexamic acid or progestins used for
12 uncomplicated HMB are inappropriate for the specified population – women with fibroids 3 cm
13 or more in diameter. The effectiveness of these treatments would have to be extrapolated from
14 studies on women with heavy menstrual bleeding without fibroids, and these medical treatments
15 may work less well for heavy menstrual bleeding associated with fibroids, which would
16 undermine the robustness of the economic modelling.

17 **Structure and Comparators**

18 The cycle length of the model was 28 days. The structure of the model was effectively a
19 decision tree where patients spent three cycles in treatment and two cycles where treatment
20 was discontinued (the 'off treatment' period).

21 Three scenarios were examined as the 'no treatment' comparator. The first was a 'no resolution'
22 arm, where HMB simply persisted for the time horizon of the model, the second and third
23 included a probability for symptoms to resolve (taken from the placebo arm of Donnez 2012)
24 instantly or gradually over 3 months. The base case comparator was taken to be the third
25 scenario, where some patients' symptoms resolved gradually as the committee felt this reflected
26 the evidence and their clinical experience.

27 The effectiveness of the intervention was modelled as the difference in health related quality of
28 life between women on and off treatment. These quality of life values were calculated using an
29 equation that linked levels of pain and blood loss reported in the trials to EQ-5D scores in the
30 base case, although a variety of other plausible values were obtained from the literature and
31 examined in sensitivity analysis (for more information on these calculations see the sections on
32 'QALY Calculations' and 'Effectiveness' below). Diagram 1 shows a diagram of the model.

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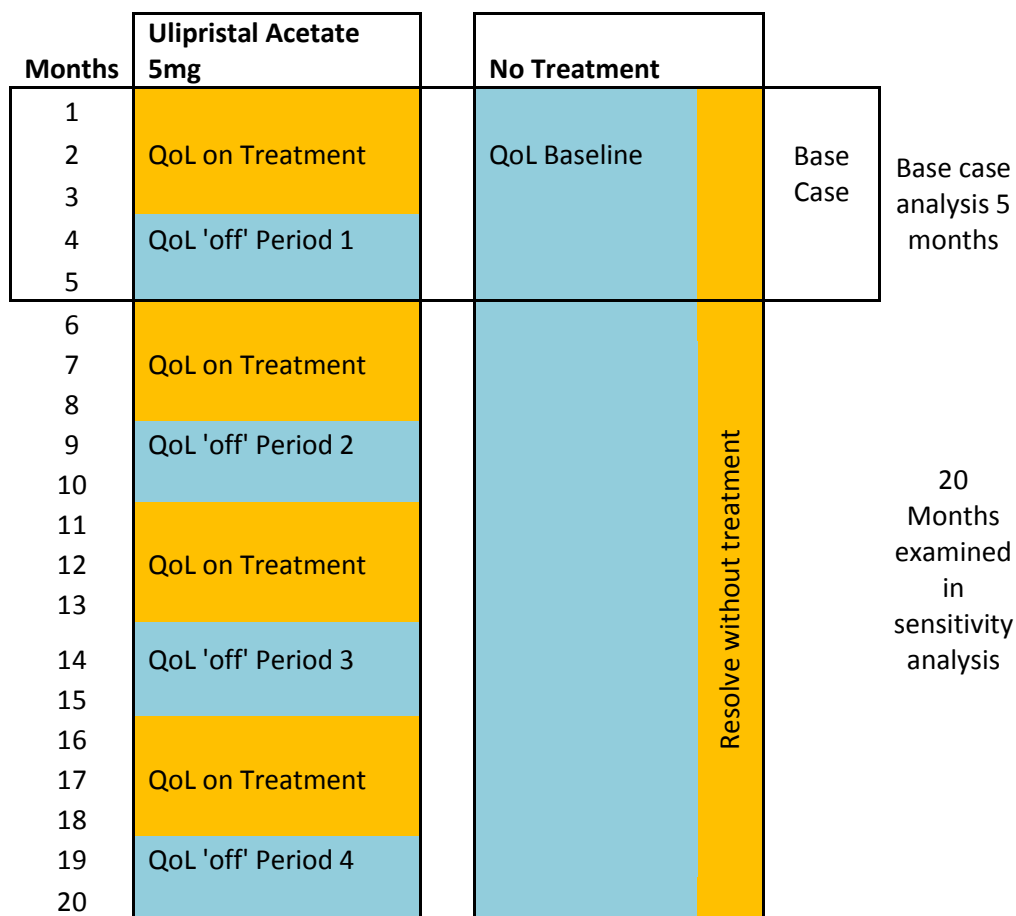
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4 Diagram 1: Diagram of the model

5 Cost calculations

6 The costs associated with ulipristal acetate treatment were believed to be the drug itself, one
7 ultrasound scan to monitor endometrial thickness and an outpatient consultant appointment
8 every 2 treatment courses on average although the exact number was highly uncertain so was
9 examined in sensitivity analysis. The monthly cost of ulipristal acetate treatment was the cost of
10 one 5mg tablet multiplied by 365 and divided by 12. .

11 QALY calculations

12 Health Related Quality of Life (HRQoL) data for treated and untreated HMB were derived from
13 the data on Pictorial Blood Loss Assessment Chart (PBAC) and Pain Scores (VAS – Visual
14 Analogue Scale) reported in Donnez 2016 (data displayed in Table M.1 below) using the
15 regression in Geale 2015. This method was chosen because relevant HRQoL values measured
16 using NICE's preferred EQ-5D instrument were not reported in the literature and this was the
17 only publically available algorithm that mapped to the EQ-5D. Means and standard errors for
18 utility at different points in the treatment pathway were obtained by resampling data generated
19 using this regression. Only the median PBAC and VAS scores were used and variability was

expressed using the standard errors of the regression coefficients. Median PBAC and VAS data were reported with wide interquartile ranges. It was decided that these ranges in the underlying patient data should not be built into the assessment of uncertainty via probabilistic sensitivity analysis as NICE's methods prescribe a focus on the cost-effectiveness for the average patient and this would introduce a high amount of uncertainty into the model that would require complex methods to manage. The mean PBAC value for the 3rd 'off-treatment' period was interpolated as the average of the off period before and after. The utilities obtained through this method were broadly consistent with those found elsewhere in the published literature (PregLem 2010). Any published data that differed substantially were investigated through deterministic sensitivity analysis. Table M.1 (in the Parameters section below) shows the intermediate outcome data used in the EQ-5D equations.

12 Cost-effectiveness calculations

The model was a cost-utility analysis where the difference in costs was divided by the difference in QALYs to calculate an Incremental Cost Effectiveness Ratio (ICER). Interventions that have ICERs of less than £20,000 per QALY are usually considered cost-effective by NICE.

16 Time horizon and discounting

The timeframe of the model is 5 months in the base case, with sensitivity analysis of up to 20 months. Following the Committee's advice, one full treatment with ulipristal acetate was assumed to include four cycles of 3 months with a 2 month break between each (the efficacy of repeated treatment courses of ulipristal acetate was evaluated in trials assessing up to four intermittent 3-month treatment courses in patients with heavy menstrual bleeding associated with uterine fibroids). The Committee was of the view that this can be expected to be the average treatment.

The Committee discussed whether a longer time horizon would be more appropriate, but decided against it, as there is no data to inform the long term consequences of ulipristal acetate beyond the selected time period. Consequently, due to the short time horizon, discounting has not been applied.

28 Perspective

For costs, the perspective of the NHS was adopted to comply with the methods set out in *Developing Guidelines: The Manual October 2014*. Consequently, the cost of lost working days and reduced productivity are outside the boundaries of this perspective and not included to the degree that they are not already accounted for in the calculation of quality adjusted life years. The perspective of people with HMB was adopted for health benefits.

M.34 Parameters

35 Effectiveness

Effectiveness was measured as the change in HRQoL at various points in the treatment pathway. The method used to derive HRQoL was explicitly based on control of bleeding and pain and the committee therefore thought that it captured the most important outcomes of interest for which there was evidence reported in the literature. Effectiveness was assumed to occur within a few days in line with the evidence reported in Donnez 2015 and the committee's advice, so resolution of symptoms was modelled as instantaneous rather than gradual.

1 No adverse events were included within the modelling as there were no available data and
 2 surgery will not be considered as firstly, there were no data, and secondly because its inclusion
 3 would necessitate a long term model, for which other outcome data of interest, such as
 4 hyperplasia are lacking. Reduction in fibroid size was not included as the Committee has
 5 advised that the primary outcome of interest is resolution of symptoms of HMB and this can
 6 occur with and without reduction in fibroids – no subgroup analysis was identified that could
 7 help address this.

8 The evidence in Donnez 2016 indicates that there is some 'retained benefit' during the month
 9 long breaks in longer term treatment. The committee's experience was that HMB symptoms
 10 would return quickly once patients stopped taking UA, however. Scenarios with and without this
 11 retained HRQoL benefit were therefore explored in sensitivity analysis. A scenario where UA
 12 was assumed to be ineffective in a proportion of patients was also examined in order to correct
 13 for the fact that median, rather than mean, data were reported in Donnez 2016 and these data
 14 would likely have had a skewed distribution that favoured treatment.

15 Utility values were obtained using the data on PBAC and VAS Pain score reported at the
 16 relevant time points in Donnez 2016 and the EQ-5D linear regression equation reported in
 17 Geale 2015. Probability distributions (and associated standard errors for use in probabilistic
 18 sensitivity analysis) were generated for these values using the standard errors of the beta
 19 coefficients in the regression equation. The equation is as follows:-

20 **EQ-5D = 0.91641 - 0.0001183(PBAC) - 0.00436(VAS)**

21 Table M.1: Intermediate outcomes used in EQ-5D calculations

Time Points in Trial	VAS (Pain)	PBAC (Blood Loss)
Baseline Donnez 2015/2016	39.5	224.0
On Treatment	7.0	77.5
After Off Period 1	22.5	123.0
After Off Period 2	15.0	92.0
After Off Period 3	10.0	84.8
After Off Period 4	13.0	77.5

22

23 This method of EQ-5D calculation was subject to some uncertainty, given that the regression
 24 has only been published as a journal abstract and in a conference presentation so the utility
 25 values associated with the different time points in the model and the retention of utility benefits
 26 in off-treatment cycles of the model were the subject of sensitivity analysis. Values were
 27 obtained from other papers in the literature that reported difference in HRQoL between patients
 28 with and without HMB symptoms and represented quite a wide range. The data used in the
 29 original guideline CG44 were used as part of these sensitivity analyses.

30 The number of consultant visits to monitor for endometrial thickening was uncertain. It was
 31 therefore assumed to be one visit every two cycles on average and varied from one every cycle
 32 to one every four cycles in sensitivity analysis. Costs of GP appointments were not included as
 33 it was not possible for the committee to quantify the number of consultations that would be
 34 necessary in each arm of the model and whether either arm would have the higher resource
 35 use.

36 Standard errors for costs were assumed to be ¼ of the average. This is in line with methods
 37 used in other NICE guidelines.

1 Table M.2: Parameter Values

Parameters	Value	SE	Distribution	Source
Probability of effectiveness - UA	0.91	0.03	Beta	Donnez 2012
Probability of effectiveness - no treatment	0.19	0.06	Beta	Donnez 2012
QoL on Treatment	0.87	0.01	Beta	Donnez 2016/Geale 2015
QoL HMB (baseline)	0.71	0.03	Beta	Donnez 2016/Geale 2015
QoL off Period 1	0.80	0.02	Beta	Donnez 2016/Geale 2015
QoL off Period 2	0.84	0.01	Beta	Donnez 2016/Geale 2015
QoL off Period 3	0.86	0.01	Beta	Donnez 2016/Geale 2015
QoL end Period 4	0.85	0.01	Beta	Donnez 2016/Geale 2015
Cost of consultant visit (Outpatient Gynaecology)	120.00	30.00	Gamma	NHS Reference Costs 14/15
Cost of ultrasound scan	52	13.00	Gamma	NHS Reference Costs 14/15
Cost of UA Pack of 28 tablets * 5 mg	114.13	28.53	Gamma	BNF Oct 2015
Number of consultant visits per 3 month course of treatment	0.5	-	-	Assumption

2

M.4.3 Deterministic sensitivity analyses

4 Alternate Utility Values

5 A range of utility values were reported in the literature. The values with the highest and lowest
6 ranges between treated and untreated HMB were used to test the sensitivity of the model.
7 These values were 0.84 and 0.5 from NICE CG44 and 0.83 and 0.718 reported in PregLem
8 2010. These latter values were mapped using an algorithm that was unavailable in the
9 published literature at the time of writing (Rowen and Brazier 2011). Values for 'off treatment'
10 retained benefit within the model were interpolated using these ranges and the base case data.

11 Table M.3 – Alternate utility values

Parameters	Value	Source
PregLem 2010 Interpolated QoL on Treatment	0.83	Max/Min from Preglem 2010, Interpolated using Donnez 2016
PregLem 2010 Interpolated QoL HMB (baseline)	0.72	
PregLem 2010 Interpolated QoL off Period 1	0.78	
PregLem 2010 Interpolated QoL off Period 2	0.81	
PregLem 2010 Interpolated QoL off Period 3	0.83	
PregLem 2010 Interpolated QoL end Period 4	0.82	
Tsoi 2015 Interpolated QoL on Treatment	0.73	Max/Min from Tsoi 2015, Interpolated using Donnez 2016
Tsoi 2015 Interpolated QoL HMB (baseline)	0.55	
Tsoi 2015 Interpolated QoL off Period 1	0.66	
Tsoi 2015 Interpolated QoL off Period 2	0.70	
Tsoi 2015 Interpolated QoL off Period 3	0.72	
Tsoi 2015 Interpolated QoL end Period 4	0.71	
CG44 Interpolated QoL on Treatment	0.84	Max/Min from

CG44 Interpolated QoL HMB (baseline)	0.50	CG44, Interpolated using Donnez 2016	
CG44 Interpolated QoL off Period 1	0.70		
CG44 Interpolated QoL off Period 2	0.78		
CG44 Interpolated QoL off Period 3	0.83		
CG44 Interpolated QoL end Period 4	0.80		

1

2 Further sensitivity analyses were conducted assuming no retained benefit off treatment and
3 then assuming that the effectiveness of UA was only 91% (value sourced from active arm of
4 Donnez 2012 to correct for the potential bias in using median values for intermediate outcomes
5 – see 'Effectiveness' section above). The base case results table (M.4) also shows the cost-
6 effectiveness of UA versus no treatment where the 18.8% of patients instantly resolve and
7 where 0% of patients resolve was also undertaken. Sensitivity analysis with a greater resolution
8 rate was not undertaken as the committee noted that 18.8% spontaneous resolution of
9 symptoms in this condition (which would already likely be long term) appeared high.

10 There was some uncertainty regarding the number of consultant visits necessary to monitor
11 endometrial thickening so sensitivity analyses were conducted assuming 1 per cycle and 1 per
12 4 cycles.

13

M.54 Probabilistic sensitivity analysis

15 The probability distributions included in table M.1 were assigned to the relevant model
16 parameters. The model was then re-run 5,000 times, resampling data from the relevant
17 distributions and the resulting ICERs were recorded.

M.68 Results

19 Base Case Results

20 Table M.4 shows the results of the base case analysis. This analysis compares ulipristal acetate
21 treatment with 3 separate assumptions about resolution of symptoms in the 'no treatment' arm
22 (No Resolution, Immediate Resolution and Gradual Resolution). Of these arms, gradual
23 resolution was thought to be the most reasonable base case by the committee.

24

25 Table M.4 Base Case Results (1 Treatment Cycle)

26

Strategy - 1 Course Base Case	Costs	QALYs	Inc Costs	Inc QALYs	ICER (£/Q)	% C/E
NT - No Resolution	£0	0.2727				
NT - Immediate Resolution	£0	0.2827				
NT - Gradual Resolution (one cycle)	£0	0.2788				
Ulipristal Acetate 5mg	£454	0.3234				
UA vs NT - No Res (Deterministic)			£454	0.05	£8,955	
UA vs NT - Instant Res (Deterministic)			£454	0.04	£11,166	

Clinical Guideline 44.1 Heavy menstrual bleeding

Cost-utility analysis of ulipristal acetate vs no treatment for the treatment of fibroids 3 cm or more in diameter

UA vs NT - Gradual Res (Deterministic)			£454	0.04	£10,183	
UA vs NT - NR (Probabilistic)*			£453	0.05	£8,924	98.9%
UA vs NT - IR (Probabilistic)*			£453	0.04	£11,157	95.1%
UA vs NT - GR (Probabilistic)*			£453	0.04	£10,166	97.3%

1

2 Table M.5 Base Case Results (4 Treatment Cycles)

Strategy - 4 Courses Base Case	Costs	QALYs	Inc Costs	Inc QALYs	ICER (£/Q)	% C/E
NT - No Resolution	£0	1.0906				
NT - Immediate Resolution	£0	1.1308				
NT - Gradual Resolution (one cycle)	£0	1.1269				
Ulipristal Acetate 5mg	£1,662	1.3154				
UA vs NT - No Res (Deterministic)			£1,662	0.22	£7,393	
UA vs NT - Instant Res (Deterministic)			£1,662	0.18	£9,003	
UA vs NT - Gradual Res (Deterministic)			£1,662	0.19	£8,815	
UA vs NT - NR (Probabilistic)*			£1,664	0.23	£7,370	99.9%
UA vs NT - IR (Probabilistic)*			£1,664	0.19	£8,980	99.4%
UA vs NT - GR (Probabilistic)*			£1,664	0.19	£8,793	99.6%

3

4 If QALYs are valued at £20,000, treatment with UA appears cost effective from the NHS
5 perspective. The results of the PSA confirm the stability of these results, with very similar
6 average ICERs and a high proportion (almost 100%) of re-runs of the model having ICERs
7 below £20,000/QALY.

8 The results were also robust with respect to assumptions around the resolution rate on the 'no
9 treatment' arm. The committee noted that the base case 18.8% resolution rate on 'no treatment'
10 was higher than expected, as the results showed that the ICER only changed by ~£1,600
11 assuming a zero rate, further sensitivity analyses on this parameter (including those favouring
12 no treatment) were not needed.

13 Sensitivity Analyses

14 The results of the deterministic sensitivity analyses are reported in table M.6 below.

15 Table M.6 Deterministic Sensitivity Analyses

16

SA vs Gradual Resolution (1 Treatment Cycle)	Inc Costs	Inc QALYs	ICER (£/Q) 1 Course	ICER (£/Q) 4 Courses
UA (Base Case)	£454	0.0446	£10,183	£8,815
UA (Utils from CG44)	£454	0.0957	£4,748	£4,110
UA (Utils from Tsoi 2015)	£454	0.0507	£8,968	£7,763
UA (Utils from PregLem 2010)	£454	0.0315	£14,41	£12,47

Clinical Guideline 44.1 Heavy menstrual bleeding

Cost-utility analysis of ulipristal acetate vs no treatment for the treatment of fibroids 3 cm or more in diameter

			2	6
UA (Base Case Utils - 91% Effective)	£454	0.0398	£11,413	£9,938
UA Utils from CG44 2010 / 91% Eff	£454	0.0854	£5,321	£4,633
UA Utils from Tsoi 2015 2010 / 91% Eff	£454	0.0452	£10,050	£8,751
UA Utils from PregLem 2010 / 91% Eff	£454	0.0281	£16,152	£14,064
UA (Base Case Utils - Benefit not retained)	£454	0.0304	£14,968	£15,153
UA (Utils from CG44 / Benefit not retained)	£454	0.0651	£6,978	£7,064
UA (Utils from Tsoi 2015 / Benefit not retained)	£454	0.0345	£13,181	£13,344
UA (Utils from PregLem 2010 / Benefit not retained)	£454	0.0215	£21,183	£21,445
UA (Base Case Utils / Benefit Not Retained / 91% Effective)	£454	0.0269	£16,891	£17,339
UA (Utils from CG44 / Benefit not retained, 91% Eff)	£454	0.0577	£7,874	£8,083
UA (Utils from Tsoi 2015 / Benefit not retained, 91% Eff)	£454	0.0305	£14,874	£15,268
UA (Utils from PregLem 2010 / Benefit not retained, 91%Eff)	£454	0.0190	£23,904	£24,538
UA Base case Utils / 1 Extra Ultrasound	-	-	-	£9,091
UA Base case Utils / Average 1 consultant visit per year	£424	0.0446	£9,511	£8,179
UA Base case Utils / Average 4 consultant visits per year	£514	0.0446	£11,528	£10,089
UA Calendar Month (3:1 regimen)	£484	0.0429	£11,279	£10,428
UA Calendar Month (3:1 regimen) / Benefit not retained	£484	0.0352	£13,764	£13,921

1 The results of the model were robust to the deterministic sensitivity analyses conducted with the
2 exception of the most pessimistic scenarios (Utils from PregLem 2010 / Benefit not retained

3). This ICER would reduce below £20k/QALY if the resolution of symptoms without treatment
4 decreased. It was noted that the assumption of 18.8% spontaneous resolution in the no
5 treatment arm made between £5k-£6k/Q difference to these high ICERs. The committee were
6 uncertain about what the appropriate level of spontaneous resolution would be in the 'no
7 treatment' arm but noted that 18.8% is likely high, given the enduring nature of HMB symptoms
8 in this patient group.

9 The ICER was relatively insensitive to the number of consultant visits, ranging between £9,500 -
10 £11,500. It would therefore be highly likely to be insensitive to assumptions regarding GP visits
11 if these were found to differ between the arms as the cost of GP visits is lower than the cost of
12 consultant visits. The ICER was also insensitive to assuming the cost of an extra ultrasound for
13 monitoring in the 4-cycle analysis. The committee noted that the cost of follow up consultant
14 visits might be less than that used in the model, but due to the insensitivity of the model to these
15 costs, sensitivity analysis was not conducted.

16 The choice of 28 days versus calendar months and the 3:2 regimen versus the 3:1 regimen
17 were shown to have small effects on the ICERs, with the latter having a larger effect. If benefit

was assumed to be retained in 'off treatment' periods then the ICER went down as the total time horizon of the model was longer and therefore the time the arms spent with different QoL values was greater. If no benefit was assumed to be retained the ICER went up due to the people who spontaneously resolve becoming comparatively more important in the analysis.

Table M.7 Comparison of ICERs under different treatment regimes

Analysis	Calendar Month (3:1)	28-Day (3:2)
UA 1 Cycle	£11,279	£10,183
UA 1 Cycle No Retained Benefit	£13,764	£14,968
UA 4 Cycles	£10,428	£8,815
UA 4 Cycles No Retained Benefit	£13,921	£15,153

6

M.7.7 Discussion

This cost effectiveness analysis found that ulipristal acetate is a cost-effective treatment for heavy menstrual bleeding in women with fibroids of 3 cm or more when compared to no treatment. The results were driven by the increased utility associated with reduction in pain and increased control of blood loss. These results were found to be robust with respect to parameter uncertainty in probabilistic sensitivity analysis.

Various deterministic sensitivity analyses were tested in the model, particularly assumptions regarding utility associated with controlled and uncontrolled bleeding and the retention of benefit in 'off treatment' months. While the ICER was sensitive to changes in these values, sensitivity analyses had ICERs below £20,000 per QALY in all but the most pessimistic scenarios.

While no explicit sensitivity analyses were undertaken, the results of the model suggest that there would be considerable uncertainty about the cost effectiveness of ulipristal acetate 10mg in this population as the cost of the drug was the main driver of costs in the model.

Limitations of the model

The model built for this review question only assessed ulipristal acetate in comparison to no treatment for the intermittent short term control of HMB in women not currently considering surgery. It was the committee's view that, as ulipristal acetate does not appear to provide a long term solution to HMB (as with surgical and radiological procedures), this population would be quite small. Due to lack of available data, the model did not include any adverse events such as endometrial thickening. The committee noted that the population from which the data that populate this model were drawn were highly selected individuals awaiting surgery. They would therefore likely have symptoms more severe than the population to which the recommendation applies and the effectiveness and cost-effectiveness results produced by the model would therefore likely be optimistic.

31

M.8.2 HE References

PregLem, 2010. A Phase III, randomized, parallel group, double-blind, double-dummy active comparator-controlled, multi-center study to assess the efficacy and safety of PGL4001 (ulipristal) versus GnRH-agonist (leuporelin 3.75mg) for pre-operative treatment of symptomatic uterine myomas.

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- 3 Donnez et al 2016 Long-term medical management of uterine fibroids with ulipristal acetate.
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