

Heavy Menstrual Bleeding

Consultation on draft guideline - Stakeholder comments table 12/05/2016 to 10/06/2016

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ID	Type	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
1	SH	Primary Care Women's Health Forum	Short	9	General	UPA side effects – uterine haemorrhage listed as a common and a less common side effect.	Thank you for spotting this error which has now been corrected. Uterine haemorrhage is now listed as a less common adverse effect.
2	SH	Primary Care Women's Health Forum	Short	22	11	This is an important question and one that will be the biggest restricting concern – need to demonstrate that long term safety is good. And provide examples of shared-care pathways or best practice examples of how repeated courses should be provided, what assessments are necessary before starting a repeat course if the problem recurs after a short or longer time period.	Thank you for your comment,
3	SH	Primary Care Women's Health Forum	Short	general	general	The economic argument to support longer term use is important. Costing in repeat scans/endometrial sampling. Examples of shared pathways and formulary decisions will support the use of UPA as an alternative option to more invasive procedures.	Thank you for your comment. An extra sensitivity analysis was conducted on the 4-course analysis in the decision model, including the cost of an extra ultrasound scan for monitoring. This analysis showed that the extra scan had a very small effect on the results of the cost effectiveness analysis.
4	SH	Clinical Effectiveness Unit of the Faculty of Sexual and Reproductive	Addendum	8	general	Ulipristal acetate is a welcome addition to the range of therapeutic options for treatment of heavy menstrual bleeding.	Thank you for your comment

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		Healthcare					
5	SH	Clinical Effectiveness Unit of the Faculty of Sexual and Reproductive Healthcare	Addendum	10	general	The terminology of 'offer' and 'consider' are not that helpful in this context and these could be merged into a single recommendation. Basing this on a single haemoglobin measurement is artificial in clinical practice and may only reflect the stage at which the woman is presenting.	Thank you for your comment. The committee considered that the recommendations should reflect the strength of the evidence base. As one of the included studies used anaemia as one of the criteria for inclusion and this studies provided high quality evidence for a critical outcome (menstrual blood loss) then an 'offer' recommendation was deemed appropriate. The committee also considered that women may take supplement (such as iron) to avoid anaemia and it would be disadvantageous to women with heavy menstrual bleeding and fibroids > 3 cm not to have a recommendation for these women. However the committee noted that the evidence base for this population was not strong and so a 'consider' recommendation was deemed appropriate.
6	SH	Clinical Effectiveness Unit of the Faculty of Sexual and Reproductive Healthcare	Addendum	18	general	The evidence base to support use of mifepristone as a treatment for heavy menstrual bleeding is not robust and we agree this should not be used in clinical practice.	Thank you for your comment We have noted in the Evidence to recommendations table that "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."
7	SH	Clinical Effectiveness	Addendum	general	General	Ulipristal acetate is hardly used for treatment of heavy menstrual bleeding and it should be promoted more for	Thank you for your comment.

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		Unit of the Faculty of Sexual and Reproductive Healthcare	nd u m		al	suitable women following this NICE review of its effectiveness. Trusts should be encouraged to include it in local formularies as a cost effective option and alternative to surgery.	
8	SH	British Society for Gynaecological Endoscopy	Ad de nd u m	gene ral	ge ner al	The British Society for Gynaecological Endoscopy is pleased to see part of the guidelines on heavy menstrual bleeding (HMB) being updated. However we would urge the NICE to update the rest of the guidelines, as there has been a significant amount of new information added to the current literature since 2007.	Thank you for your comment. The full guideline is in the process of being updated (https://www.nice.org.uk/guidance/indevelopment/gid-ng10012)
9	SH	British Society for Gynaecological Endoscopy	Ad de nd u m	gene ral	Ge ner al	It is timely to add Ulipristal acetate as a long term intermittent medical treatment option for HMB. However, the first indication of ulipristal acetate for presurgical treatment of fibroids has been left out, despite the fact that there are two high quality randomised control trials supporting its use for this indication.	Thank you for your comment. The committee noted in the Evidence to recommendations table 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. The guideline has an existing recommendation to cover this point 1.5.13 “Use of a gonadotrophin-releasing hormone analogue could be considered prior to surgery or when all other treatment options for uterine fibroids, including surgery or

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							uterine artery embolisation, are contraindicated. If this treatment is to be used for more than 6 months or if adverse effects are experienced then hormone replacement therapy 'add-back' therapy is recommended."
10	SH	British Society for Gynaecological Endoscopy	Addendum	general	general	The table on the side effects of treatments option gives the impression that ulipristal acetate has many more side effects in comparison to other medical treatment options, particularly compared to GnRHa. This is most likely due to the threshold for inclusion of side effects in 2007 being different than the current threshold. In clinical practice and in the RCT comparing UPA with GnRHa, the side effects are clearly less with UPA. The table probably gives an unfair impression.	Thank you for your comment. The information contained in this table (with exception of ulipristal acetate) dates from the 2007 guideline. This is in the process of being updated (https://www.nice.org.uk/guidance/indevelopment/gid-ng10012)
11	SH	British Society for Gynaecological Endoscopy	Addendum	2.6	general	The addendum states that there was no reduction in surgery rates with UPA treatment for 13 weeks. This is inappropriate as the RCT was not designed to compare the reduction in surgery rates, on the contrary, the patients included were lined up to undergo surgery but some of these decided not to proceed with surgery due to improvement of their symptoms.	Thank you for your comment. The committee noted in the evidence statements that the data on surgical rates for UPA versus placebo were inconclusive and there was no difference for the comparison of UPA versus leuporelin acetate as this is what the data shows. However the committee noted in the Evidence to recommendations section that the data on surgical rates were limited as follows "It was noted that ulipristal acetate was not associated with a reduction in surgery rates after 13 weeks of treatment

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							(although reduced surgery rates were not an aim of treatment in the study), and there was no evidence on surgery rates after more than one treatment cycle."
12	SH	NHS England	general	general	general	No comments	Thank you
13	SH	Gedeon Richter	Short	9	1	<p>For the 'Potential unwanted outcomes experienced by some women'/side effect profile information, we would like to bring to your attention that 'menstrual disturbances' is not listed in the ulipristal acetate (UPA) 5mg Summary of Product Characteristics (SPC); uterine haemorrhage is only listed under 'uncommon' in the UPA 5mg SPC.</p> <p>We note that all the side effects which are listed in the UPA 5mg SPC are included in this draft document whilst the same is not true for the other treatments in this document (we do acknowledge however that the other recommendations in grey are not being updated at the present time)</p>	<p>Thank you for spotting this error which has now been corrected, Menstrual disturbances has now been removed from the list of adverse effects of ulipristal acetate.</p> <p>Thank you for your comment. The information contained in this table (with exception of ulipristal acetate) dates from the 2007 guideline. This is in the process of being updated (https://www.nice.org.uk/guidance/indevelopment/gid-ng10012)</p>
14	SH	Gedeon Richter	Short	11	9	The new sub-heading 'Fibroids less than 3 cm in diameter' could be clearer and state 'Fibroids less than 3 cm in diameter and where no fibroids are present' since the next sentence covers both these groups	Thank you for your comment. This has been amended as suggested.

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15	SH	Gedeon Richter	Short	12	19-25	<p>New section 'Fibroids 3 cm or more in diameter' and the slightly different recommendations based upon haemoglobin (Hb) level</p> <p>We would like to bring to your attention that the efficacy evidence for UPA in symptomatic fibroids comes from 4 phase III studies; a Hb level of 102g/litre was an inclusion criteria in just one of these studies (PEARL I, single 3-month course of UPA); the other studies - Pearl II, PEARL III and its extension and PEARL IV included patients with no specific Hb requirement for inclusion (thus providing a % of patients with Hb above 102g/l in these studies) and demonstrated efficacy in this population.</p> <p>In PEARL III, the median Hb value at baseline was 12.5g/dl (see PEARL III publication http://www.fertstert.org/article/S0015-0282(14)00146-0/fulltext)</p> <p>In PEARL IV, the median Hb value at screening was 12.55 g/dl and 12.40 g/dl for subjects from the 5- and 10-mg groups, respectively. (see PEARL IV publication http://www.fertstert.org/article/S0015-0282(15)01960-3/fulltext)</p>	<p>Thank you for your comment. The committee considered that the recommendations should reflect the strength of the evidence base. As one study used anaemia as one of the criteria for inclusion and this studies provided high quality evidence for a critical outcome (menstrual blood loss) then an 'offer' recommendation was deemed appropriate for this population (rec 1.5.12).</p> <p>The committee also considered that women may take supplement (such as iron) to avoid anaemia and it would be disadvantageous to women with heavy menstrual bleeding and fibroids > 3 cm not to have a recommendation for these women. However the committee noted that the evidence base for this population was not strong and so a 'consider' recommendation was deemed appropriate (rec 1.5.12).</p>

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						<p>In view of the above, we feel the recommendation to use UPA should cover all women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter</p> <p>Moreover, the UPA 5mg SPC does not specify any Hb criteria to be considered for the use of UPA</p>	
16	SH	Gedeon Richter	Short	12	19 25	<p>New section 'Fibroids 3 cm or more in diameter' and the restriction of UPA 5mg to 4 courses:</p> <p>The UPA 5mg SPC does not restrict the number of courses of UPA which can be prescribed/used; the intermittent licence was approved in May 2015 based on data of repeated use of UPA and removed the previous 2 course restriction from the SPC; furthermore, we have had a recent update to the SPC which now includes safety data for up to 8 courses of UPA treatment (please see 'Section 4.8 Summary of the safety profile and Section 5.1 Pharmacodynamic properties - Endometrial findings' of the April 2016 SPC which can be found at http://www.medicines.org.uk/emc/medicine/26068). This additional data is from the 2nd extension of the PEARL III study which will be published later this year.</p>	<p>Thank you for your comment. The committee reflected on the efficacy and safety evidence from the included studies which included up to 4 courses of ulipristal acetate. The committee also consulted the SPC and noted that it states that 446 women were exposed to four intermittent treatment courses and 53 were exposed to eight intermittent treatment courses so the data for 8 courses is still limited. Consequently, the committee were minded to retain the essence of this statement but reworded it to say the following</p> <p>"2 Offer ulipristal acetate 5 mg (up to 4 courses) 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]</p> <p>3 Consider ulipristal acetate 5 mg (up to 4 courses) for women</p>

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						<p><u>The Committee's view is that the average treatment can be expected to be 4 courses of UPA (as per the Full version of the draft guideline, pg 149, section on Time horizon and discounting). Therefore it is acknowledged that treatment can be longer than 4 courses. We are also aware that some clinicians have prescribed more than 4 courses to their patients based on clinical benefit. We appreciate this is not RCT evidence but restricting the number of courses would likely mean that those patients for whom longer treatment may be of benefit would be denied this option.</u></p> <p><u>We hope therefore that such restriction is not among the final recommendations.</u></p>	with heavy menstrual bleeding and fibroids of 3 cm or more in diameter, and a haemoglobin level above 102 g per litre. [new 2016]"
17	SH	Gedeon Richter	Short	General	General	<p>As per the UPA 5mg SPC, UPA is indicated for pre-operative and intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The pre-operative use licence has not been mentioned in the document.</p> <p>An additional sentence/recommendation to consider UPA prior to surgery would be beneficial for those women with uterine</p>	Thank you for your comment. The committee also noted that "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

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						<p>fibroids undergoing an interventional procedure.</p> <p>We are aware that the Committee has acknowledged the pre-operative indication since it is mentioned in the Committee discussion on pg 20 of the Full version under 'Trade-off between benefits and harms'; however the other benefits of UPA in terms of lesser side effects compared to gonadotropin releasing hormones and control of menstrual bleeding prior to surgery are important outcomes for a woman awaiting surgery, and therefore an additional recommendation regarding the pre-operative use of UPA would certainly be of benefit to the patients and the clinical community allowing them the choice of using UPA pre-operatively.</p> <p>A significant number of women have already benefitted from pre-operative use of UPA since its initial licence in 2012. Offering UPA would also allow patient choice after a course – either to continue medical treatment or proceed to surgery.</p> <p>NB: This additional wording could affect interpretation of the current sections 1.5.13 and 1.7.8 which have not been updated at the present time.</p>	<p>or myomectomy if the uterus is large or distorted.” The committee on further deliberation was unable to add an extra recommendation in the absence of new evidence in this population.</p>

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18	SH	Gedeon Richter	Short	22	17 18	<p>The statement that current evidence for UPA repeated treatment covers a period of 16 months is incorrect since the 4 courses treatment in PEARL III and PEARL IV covered a period of 21 months at least; the schedule is 3 months treatment followed by a break of approximately 2 months each time; thus 3+2+3+2+3+2+3+3mths follow up = 21 months</p> <p>The current wording is likely to imply to the clinical community that the break between each 3-month course of UPA is just 1 month.</p> <p>The UPA SPC states that 'Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion.' (also see comment 8 below)</p> <p>If clinicians were to use repeated courses of UPA with just a 1-month break between each course, this will be considered off-label/off-licence and as the manufacturer of UPA 5mg, we would be uncomfortable with such a recommendation which is inconsistent with the UPA SPC.</p> <p>Additionally, safety data for 8 courses of UPA has recently</p>	<p>Thank you for your comment.</p> <p>In addition, the decision model has been updated to include 2 months off treatment in the base case. While the results of the cost effectiveness analysis were not greatly affected, the results of the new analysis were presented to the committee and considered in the forming of recommendations.</p> <p>The committee also consulted the SPC and noted that it states that '446 women were exposed to four intermittent treatment</p>

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						been added to the UPA SPC (see comment 4 above)	<p>courses and 53 were exposed to eight intermittent treatment courses so the data for 8 courses is still limited so the committee were minded to retain the essence of this statement but reworded it to say the following</p> <p>“2 Offer ulipristal acetate 5 mg (up to 4 courses) 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]</p> <p>3 Consider ulipristal acetate 5 mg (up to 4 courses) 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]”</p>
19	SH	Gedeon Richter	Addendum	14	General	<p>We would like to bring to the Committee's notice the evidence from the PEARL III study and its extension (UPA 10mg +/- norethisterone) as possible missing evidence (see PEARL III publication http://www.fertstert.org/article/S0015-0282(14)00146-0/fulltext).</p> <p>Even though this covers only the 10mg dose, the Committee has acknowledged (on pg 18, line 38-39 of the Full version) based on the evidence presented to them that 'There was no evidence of a clinically important difference between doses for any of the reported outcomes.'</p>	<p>Thank you for your comment. The PEARL III publication was not considered for inclusion as it an observational study of UPA during the off-periods of which the study participants were randomised to either norethisterone acetate or placebo</p> <p>Pain in this study was also not measured using the VAS so was unsuitable for inclusion into the economic model.</p>

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						The 10mg repeated dose study would therefore be relevant to consider in the totality of the evidence.	
20	SH	Gedeon Richter	Addendum	16	31 33	<p>We are concerned that the decision model for this update used a cycle length of 3 months of treatment with ulipristal acetate 5mg followed by a 1 month period off treatment. This is likely to imply to the clinical community that the break between each 3-month course of UPA is just 1 month.</p> <p>This is important to note and rectify since the UPA SPC states that 'Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion.' This wording in the SPC implies approximately 2 months off treatment before the next course can be restarted.</p> <p>If clinicians were to use repeated courses of UPA with just a 1-month break between each course, this will be considered off-label/off-licence as it is not in line with the UPA SPC.</p>	Thank you for your comment. The decision model has been updated to include 2 months off treatment in the base case. While cost effectiveness was not greatly affected, the results of the new analysis were presented to the committee and considered in the forming of recommendations.
21	SH	Gedeon Richter	Addendum	17	11 12	Table 2; Cost for 3 month course of UPA 5mg = £114.13 (per 28-day pack) x3 = £342.39 (3 packs)	Thank you for your comment. The cycle length of the model has been updated to 28 days rather than calendar months to be more in line with likely clinical practice and the costs

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			u m				updated accordingly. The cost effectiveness was not greatly affected but the results were re-presented to the committee.
2 2	S H	Gedeon Richter	Ad de nd u m	19	Ge ner al	<p>Table 2.6 Evidence to recommendations Relative value of different outcomes</p> <p>With regards to the statement 'However, the topic experts noted that endometrial hyperplasia is rare, and therefore differences in endometrial hyperplasia rates between treatments were unlikely to be detected in short-term randomised controlled trials.'</p> <p>The recent update to the SPC now includes safety data for up to 8 courses of UPA treatment (please see Section 4.8 Summary of the safety profile and Section 5.1 Pharmacodynamic properties - Endometrial findings of the April 2016 SPC which can be found at http://www.medicines.org.uk/emc/medicine/26068)</p>	<p>Thank you for your comment. The SPC states that '446 women were exposed to four intermittent treatment courses and 53 were exposed to eight intermittent treatment courses so the data for 8 courses is still limited. Consequently the committee were minded to retain the essence of this statement but reworded it to say the following</p> <p>"2 Offer ulipristal acetate 5 mg (up to 4 courses) 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]</p> <p>3 Consider ulipristal acetate 5 mg (up to 4 courses) 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]"</p>
2 3	S H	Gedeon Richter	Ad de nd u m	19	Ge ner al	<p>Table 2.6 Evidence to recommendations Quality of evidence</p> <p>With regards to 'it was noted that ulipristal acetate was not associated with a reduction in surgery rates after 13 weeks of</p>	<p>Thank you for your comment, We have now amended this statement in the Evidence to recommendations as follows "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</p>

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						<p>treatment (although reduced surgery rates were not an aim of treatment in the study), and there was no evidence on surgery rates after more than one treatment cycle.'</p> <p>It was an exploratory objective to assess the incidence and type of surgery on fibroids in PEARL IV (repeated course study) and the European Public Assessment Report (EPAR) mentions that only 16 patients in the study (of 451 recruited) underwent surgery. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002041/human_med_001542.jsp&mid=WC0b01ac058001d1240).</p>	in the study and in total only 18 women out of 451 underwent surgery in one study),"
24	SH	Gedeon Richter	Addendum	26	23 24	<p>Section 3 References</p> <p>The full PEARL IV study publication (citation below) should be listed instead of the Part 1 study results paper currently mentioned.</p> <ul style="list-style-type: none"> - 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>This full paper has been used in the evidence review and is present in Appendix G Evidence tables</p>	Thank you for your comment. We have listed both references in the heading for Table 13 in Appendix G

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25	SH	Gedeon Richter	Addendum	147 150	19 21 8 9	<p>- Off treatment period in the model should be 2 months as per the UPA SPC which states that 'Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion.'</p> <p>-mentions 'month long breaks in longer term treatment' – incorrect as breaks were approximately 2 months between courses in Donnez 2016</p> <p>-Also see comment 8 above</p>	Thank you for your comment. The decision model has been updated to reflect a 3:2 regimen and the results re-presented to the committee. The cost effectiveness of UPA was not greatly affected by this change.
26	SH	Gedeon Richter	Addendum	148	7 8	Monthly cost of UPA has been calculated as the cost of one 5mg tablet multiplied by 365 and divided by 12; this is not realistic considering that the pack size is 28 days and a 3 month course will typically be 3 packs thus £114.13x3=£342.39	Thank you for your comment. The cycle length of the model has been updated to 28 days rather than calendar months to be more in line with likely clinical practice and the costs updated accordingly. The cost effectiveness of UPA was not greatly affected but the results were re-presented to the committee.
27	SH	Gedeon Richter	Addendum	149	8	<p>Section on 'Time horizon and discounting'</p> <p>The timeframe of the model is 4 courses of UPA which is the 'average treatment' in the Committee's view.</p> <p>We would like to suggest that the pharmaco-economic evaluation be extended to 8 courses since UPA does have</p>	Thank you for your comment. We have not found any published data on PBAC, VAS or any other outcomes data that would allow us to extend the economic model to 8 courses. Under the assumption that effectiveness is no worse and there are no significant adverse events associated with such an extension, we would expect the cost-effectiveness of UPA to

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						<p>safety data for up to 8 courses which should reassure the Committee about a usage for more than the average 4 courses; there would not be any assumption of increased efficacy after course 4 (thus efficacy in the model remains the same but clinically this continued efficacy would be beneficial to the patients).</p> <p>We would also like to bring to the Committee's attention that the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) have both assessed the cost effectiveness of the repeated use of UPA beyond 4 courses as part of a full Health Technology Appraisal and have recommended that UPA be used as per its intermittent licence indication. Links to the documents are below:</p> <p>https://www.scottishmedicines.org.uk/SMC_Advice/Advice/1128_16_ulipristal_acetate_Esmya/ulipristal_acetate_Esmya</p> <p>http://www.awmsg.org/awmsgonline/app/appraisalinfo/2767</p>	be similar to that of the 4 course analysis. As such, we do not believe extending the model would provide relevant evidence for the committee to consider.
28	SH	Department of Health	general	general	General	No comments	Thank you
2	S	RCOG	Ad	Gen	Ge	Thank you for the opportunity to review this guideline. The	Thank you for your comment

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9	H		document	eral	neral	Guidelines Committee and the Lindsay Stewart Committee have contributed to this feedback. We welcome the addition and inclusion of ulipristal acetate to this guideline.	
30	SH	RCOG	Ad document	1.2 1.3	8 9	Whilst we know less about the safety profile of SPRMS and specifically UPA, the PEARL I-IV RCTs (Donnez Trials) are reassuring about the risk of endometrial disease and serious side-effects. The " <i>Potential unwanted outcomes experienced by some women</i> " section seems to list a disproportionate number of specific side-effects (generally minor) for UPA compared with those listed for the more established pharmaceutical treatments. I don't know whether this is a deliberate decision given the newer nature of UPA or whether it is simply listing all those reported in the PEARL RCTs. If the side-effects reported in the British National Formulary (BNF) were listed for all pharmaceutical agents the Table would become unwieldy so sensibly this has not been done. However, the table does appear partial; for example ovarian cysts are listed as "Common" for UPA but there is no mention of them for the progestogen only treatments where such cysts are more likely too.	Thank you for your comment. The information contained in this table (with exception of ulipristal acetate) dates from the 2007 guideline. This is in the process of being updated (https://www.nice.org.uk/guidance/indevelopment/gid-ng10012)
31	SH	RCOG	Adde	1.2.1 3	Gener	Needs a comma after "45 and over" or doesn't make sense	Thank you for your comment. This has now been amended as suggested. The recommendation now reads as follows

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			nd u m		al		"1.2.13 If appropriate, a biopsy should be taken to exclude endometrial cancer or atypical hyperplasia. Indications for a biopsy include, for example, persistent intermenstrual bleeding, and in women aged 45 and over, treatment failure or ineffective treatment. [2007]"
3 2	S H	RCOG	Ad de nd u m	1.5.1 1	ge ner al	The Hb cut off is a bit odd - 102 g/l. I suspect that this is because of the evidence but would NICE consider a round number e.g.105.	Thank you for your comment. The committee decided to retain the cut-off of 102 g/l to reflect the evidence included.
3 3	S H	RCOG	Ad de nd u m	1.5 1.5.1 1 1.5.1 2	19 25	I am aware that comments should not be made on 2007 recommendations but I am not sure where the rather arbitrary '3cm' fibroid cut off arises from. This is important because the subsequent 2016 clinical and economic update on ulipristal acetate (UPA) refers to use of this new selective progesterone receptor modulator (SPRM) in relation to fibroids of >3cm (NICE have chosen to frame the clinical question as fibroids>3cm I think pragmatically to be consistent with the 2007 guideline where this threshold was employed but also because the Pearl 1 & 2 RCTs have used this fibroid size threshold as an inclusion criteria)). This will need to be addressed in the full guideline update as uterine cavity size	Thank you for your comment. You are correct the review question was worded to be consistent with the 2007 recommendations. The inclusion criteria of some RCT's in the 2007 guideline used uterine fibroids < 3cm in size as an inclusion criteria. We will forward your comment to the NICE Surveillance team for consideration when full guideline is next reviewed for updating.

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						(cavity length) is more predictive of outcomes with pharmacological or uterine sparing surgical resection / ablation of the endometrium. The size, along with the position and location, of fibroids are important when considering the indication / prognosis for surgical and radiological interventions in contrast to pharmacological ones where these fibroid parameters are less important (unless they are submucous fibroids and a levonorgestrel -releasing intrauterine device (LNG-IUS) is being considered).	
34	SH	RCOG	Addendum	725	23	<p>This table (page 7 to page 10) describes the side-effects/complications of each treatment. The adverse effects for each treatment are either symptoms or surgical complications.</p> <p>In the new section on ulipristal acetate (page 9 of 25) I am unclear why 'endometrial thickening' has been included. The woman will not be aware of this and it is my understanding that this 'thickening' is of no clinical significance. 'Amenorrhoea' has also been included yet this doesn't appear in the list of effects for GnRH analogues or endometrial ablation or hysterectomy.</p>	Thank you for your comment. The adverse effects listed in the section on ulipristal acetate has been taken directly from the SPC on http://www.medicines.org.uk/emc/
35	SH	RCOG	Addendum	1.6.5	114	Insert 'a' after uterus	Thank you for your comment. We have now amended as suggested. The recommendation now reads as follows;

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			nd u m				"1.6.5 In women with HMB alone, with a uterus no bigger than a 10-week pregnancy, endometrial ablation should be considered preferable to hysterectomy. [2007]"
36	SH	RCOG	Ad de nd u m	1.5.1 1 1.5.1 2	20 25	Could the authors please explain why there needs to be two recommendations here? Is the recommendation that ulipristal acetate should be offered/considered to/in women with heavy menstrual bleeding and fibroids of 3cm or more regardless of the haemoglobin level.?	Thank you for your comments. The committee were mindful that one of the included studies used anaemia (<102 g per litre) as an inclusion criteria and that the topic experts noted that the evidence reflected their own clinical experience. The committee agreed that it was important to have separate recommendations to reflect the strong evidence base and decided to draft an 'offer' recommendation for the use of 5mg ulipristal acetate for women with heavy menstrual bleeding and fibroids > 3cm and with anaemia. The committee then decided that there was sufficient evidence of effectiveness and importantly no strong evidence of harm to draft a 'consider' recommendation for the use of 5mg ulipristal acetate for women with heavy menstrual bleeding and fibroids > 3cm who do not have anaemia. This was to ensure that women with heavy menstrual bleeding and fibroids > 3cm who did not have anaemia are not disadvantaged by the recommendations
37	SH	RCOG	Ad de	13	75	I think the row headed 'Race' should be checked as the numbers are way short of the 228 inclusions	Thank you for spotting this error, we have now correct to state Caucasian = 211 not 12

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			nd u m				
38	SH	RCOG	Ad de nd u m	13	75	I think we should use the term 'fibroid' in the narrative for consistency and only use the terms leiomyoma or myoma (very European) if the title of the research paper uses these terms.	Thank you for your comment. We have now used the term fibroid in all cases outside of article titles and names of quality of life scales
39	SH	RCOG	Ad de nd u m	13	79 80	I wanted to be sure that the paper Tb 13 refers to shows similar populations and magnitudes of change in UFS scores/ PBAC scores as the Pearl 1 & 2 studies (Tables 11 & 12 in the Addendum). The population in Pearl 4 seems less diseased with lower PBAC scores and the magnitude of change appears must less impressive cf. Pearl 1 & 2 summarised in the preceding Tables. In addition I'm struggling to grasp the data presented for PBAC scores showing '% changes in the median from baseline scores' - is this correct?. In any case, the long term effect seems sustained (cycle 4) albeit the clinical significance is less clear with median PBAC scores >100 (a score which would still be considered in Research Trials as diagnostic of heavy menstrual bleeding – and interestingly an inclusion criteria for the Pearl 1 & 2 studies)). Scores were >100 even	Thank you for your comment. The baseline PBAC characteristics do indicate that the population in Pearl IV are less severely affected. Yes, this data is correct. We took this data from Supplementary data provided here (http://www.fertstert.org/article/S0015-0282(15)01960-3/addons) QoL in the economic model was derived via an algorithm that used PBAC and VAS scores and was the subject of extensive sensitivity analyses due to acknowledged uncertainties around the accuracy of this measure. The PBAC data in Pearl 1 & 2 potentially indicate even greater clinical effectiveness than that used in the model and taken from Pearl IV, albeit on a shorter follow up time and in a smaller sample population. The

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						<p>after the first course of treatment in contrast to Pearl 1 & 2 data presented – why is UPA apparently less effective in this study - not immediately apparent from the inclusion / exclusion criteria.</p> <p>On the other hand the baseline and follow up improvement in UFS QoL scores are consistent. Thus the reliability / validity of the PBAC may be the problem!? I note clinical recommendations are being based upon QoL.</p>	<p>conclusions of the model (that UPA is cost-effective) would therefore be unlikely to change if the more severe data were used. A note has been added to the LETR table to this effect.</p>
40	SH	RCOG	Addendum	1.5.1 1 1.5.1 2 1.2	12 11	<p>I am happy with these provisional recommendations. They seem sensible as I note the committees concerns over the generalisability of the results to a wider, probably less diseased population. The term 'offer' and 'consider' have been used for the use of UPA according to whether clinical anaemia is present (Hb 102g/L). I agree that anaemia in the presence of fibroid associated HMB is probably a good indicator of severity and its presence was used as an inclusion criteria in one (UPA vs Placebo – Pearl 1 - ? why not Pearl 2 UPA v leucoprelin) of the Pearl RCTs. However, QoL is the primary outcome to dictate recommendations (and in the cost-effectiveness analysis) according to this NICE guideline and so it seems strange that we are now introducing anaemia as the final arbiter for whether one should definitely offer or just ponder its use.</p>	<p>Thank you for your comments. The committee were mindful that one of the included studies used anaemia (<102 g per litre) as an inclusion criteria and that the topic experts noted that the evidence reflected their own clinical experience. The committee agreed that it was important to have separate recommendations to reflect the strong evidence base and decided to draft an 'offer' recommendation for the use of 5mg ulipristal acetate for women with heavy menstrual bleeding and fibroids > 3cm and with anaemia. The committee then decided that there was sufficient evidence of effectiveness and importantly no strong evidence of harm to draft a 'consider' recommendation for the use of 5mg ulipristal acetate for women with heavy menstrual bleeding and fibroids > 3cm who do not have anaemia. This was to ensure that women with heavy menstrual bleeding and fibroids > 3cm who did not have</p>

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41	SH	RCOG	Addendum	2.8	25	<p>I agree with the need for longer term follow up studies and I am aware that the 'ICON' study run by the manufacturers is looking at this in a post marketing surveillance study. However, it would be preferable to have such studies funded independently from Industry as all the data supporting UPA to date has been supported by the manufacturers.</p> <p>Why are we not making a recommendations for research in this 'HMB guideline' (it's not a fibroid guideline) into the use of UPA in HMB regardless of the presence of fibroids in light of the impressive changes in bleeding scores, inducing amenorrhoea etc. in Pearl 1-4 especially as the causative role of fibroids (which are highly prevalent) in HMB is far from clear cut?</p> <p>Although it appears to me out with the remit of the guideline, the CUA (see below) has incorporated pain scores into its effectiveness outcome in addition to quantity of bleeding (PBAC). I do believe that the SPRMs can affect changes in pelvic pain whether menstrual or not. Thus, should we be recommending future research in the pain area?</p>	<p>anaemia are not disadvantaged by the recommendations</p> <p>Thank you for your comment. The committee were mindful of the role of industry in the funding of the included studies and considered that NICE research recommendations may be shortlisted for funding by the NIHR</p> <p>The NICE process outlined in the Unified process manual (available at https://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview) only permits research recommendations in specific circumstances where we have searched for and identified no or few studies, As we have not searched for studies of ulipristal acetate in women with fibroids < 3 cm or no fibroids we are not in a position to make a research recommendation on this topic, as we do not know if such studies already exist.</p> <p>Likewise we have not searched for or reviewed evidence of the effectiveness of SPRM's on pain so we are not in a position to make a research recommendation on this topic</p> <p>Regarding the CUA, NICE's methods manual allows incorporation of data not explicitly searched for as part of the</p>

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							<p>clinical review in economic models. The VAS and PBAC algorithm was the only method identified by the technical team that could tie HMB symptoms reported in the Pearl trials to EQ-5D scores.</p> <p>The full guideline is in the process of being updated (https://www.nice.org.uk/guidance/indevelopment/gid-ng10012)</p>
42	SH	RCOG	Addendum	146 154	general	<p>I like this CUA. As always with these things the assumptions and simplifications are key and they seem reasonable. The main two issues for me are firstly that the subsequent clinical data (Pearl 4) is not 3 active treatment : one off (3:1) but 3:2 (subsequent treatment started on second 'off treatment menstruation' – Pearl 4). Thus it is likely that the QUALYS are overestimated given the recurrence of HMB with time off treatment, However, I think a 3:1 regimen is more likely down the line as the 3:2 I think was simply an overcautious approach given the uncertainties about long term use of UPA on the endometrium (and why would women want a return of HMB for 2 months on such a 3:2 protocol?).</p> <p>My second concern is the somewhat spurious conversion of QoL data using VAS (why are pain scores suddenly being incorporated? – there is not mention of these in the clinical</p>	<p>Thank you for your comment. The decision model has been updated to reflect a 3:2 regimen and the results re-presented to the committee. The cost effectiveness of UPA was not greatly affected by this change. We agree that there is high uncertainty in the PBAC and VAS algorithm derived QoL data but note that these values lie within other reported ranges for HMB. A range of sensitivity analyses with disparate values were presented to the committee to take account of this uncertainty.</p> <p>The PBAC and VAS data are included in table M.1.</p> <p>We agree that it is often difficult to interpret the totalled costs and QALYs accrued by models but have presented this analysis in a manner consistent with other economic</p>

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						<p>aspect of the guideline – its all about HMB) and PBAC to the NICE favoured utility instrument EQ-5D. There has to be uncertainty here, sensitivity analysis or not.</p> <p>I would like to see tabulated the actual PBAC and VAS scores used (?mean post-cycle 3 scores) that populated the model .</p> <p>Also I would like to see enough data in the base-case analysis table (M.4) to allow me to check /understand the ICERs without having to refer to the narrative (make it stand alone).</p> <p>Despite the above limitations, I think the assumptions / simplifications are reasonable and the findings intuitive given the Pearl data showing benefit and the £20-30K threshold for cost-effectiveness (UPA is expensive but not that expensive). If UPA starts giving women endometrial cancer then the findings will change radically but the short to medium term data is reassuring.</p>	<p>evaluations conducted here at NICE. We hope that sufficient information is included in the preceding sub-sections to allow an understanding of the key parameters that affect the ICERs.</p>
43	SH	Birmingham Clinical Trials Unit	Addendum	8	general	<p>The side effects listed here reflect those listed in the manufacturers' patient information leaflet, including endometrial thickening. However, they don't list the progesterone receptor modulator associated endometrial changes (PAEC) detailed in the summary of product characteristics. These PAECs may not cause symptoms apparent to the woman, and there is no evidence that they are premalignant. Whilst these changes are reversible after</p>	<p>Thank you for your comment. We have now added a footnote (see text below) to the recommendations reflect these concerns and the special warning outline in the SPC.</p> <p>"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."</p>

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						cessation of treatment, the mechanisms underlying the endometrial changes and their clinical significance remain uncertain. We note that these histological changes were not considered as an outcome when considering UPA.	
44	SH	Birmingham Clinical Trials Unit	Addendum	10	general	The recommendations regarding the use of UPA are clear for women with HMB, fibroids $\geq 3\text{cm}$ irrespective of haemoglobin. It is unclear whether women with HMB and no fibroids or fibroids $< 3\text{cm}$ and a haemoglobin $< 102\text{g/l}$ should be offered up to 4 courses of UPA. We consider they should not, as there is no trial evidence in this population.	Thank you for your comment. The committee decided to not recommend ulipristal acetate for women with HMB and no fibroids or fibroids $< 3\text{cm}$ and a haemoglobin $< 102\text{g/l}$ as the RCT evidence examined included very selective populations of women with moderate to severe heavy menstrual bleeding and as such the evidence base was not generalizable to the wider group of women with HMB.
45	SH	Birmingham Clinical Trials Unit	Addendum	19	General	We welcome the committee's selection quality of life as a critical outcome and a move away from an emphasis on menstrual blood loss. We do agree that endometrial hyperplasia is also a key safety outcome, albeit a rare event that most clinical trials will not be large enough to address. However, the PAEC changes observed following UPA have not been considered.	Thank you for your comment. The information contained in this table (with exception of ulipristal acetate) dates from the 2007 guideline. This is in the process of being updated (https://www.nice.org.uk/guidance/indevelopment/gid-ng10012)
46	SH	Birmingham Clinical Trials Unit	Addendum	19	General	The clinical trials of UPA are limited to women with fibroids $\geq 3\text{cm}$ so should not be generalised to any women with HMB.	Thank you for your comment. The committee agree with your statement and have not made any recommendations for women with fibroids $< 3\text{cm}$

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47	SH	Birmingham Clinical Trials Unit	Addendum	25	general	<p>Suggested additional recommendations:</p> <p>What is the efficacy of UPA 5mg for a duration 3 or more courses for women with HMB and either no fibroids/ fibroids <3cm, compared to the levonorgestrel-releasing intrauterine system?</p> <p>What is the clinical significance of PAECs in women with no fibroids or fibroids <3m?</p>	<p>Thank you for your comment. The NICE process outlined in the Unified process manual (available at https://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview) only permits research recommendations in specific circumstances where we have searched for and identified no or few studies. As we have not searched for studies of ulipristal acetate in women with fibroids < 3 cm or no fibroids we are not in a position to make a research recommendation on this topic, as we do not know if such studies already exist.</p> <p>Likewise, as we have not searched for nor reviewed the evidence for PAECs in women with fibroids < 3cm or no fibroids we are not in a position to make a research recommendation on this topic.</p>

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