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Review

Ulipristal acetate for the management of large uterine fibroids associated with heavy bleeding: a review

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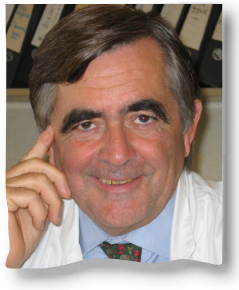

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KEY MESSAGE

Ulipristal acetate, a selective progesterone receptor modulator, significantly reduces fibroid size and controls bleeding. It also significantly improves quality of life.

A B S T R A C T

Ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRM), offers new therapeutic options for the clinical management of large uterine fibroids associated with heavy menstrual bleeding or with other moderate or severe symptoms (bulk symptoms, pelvic pain, decreased quality of life). SPRM are synthetic compounds that exert an agonist or antagonist effect on target tissues by their binding to progesterone receptors. UPA reduces fibroid size, controls bleeding in a high percentage of women and significantly improves quality of life. The present review aims to provide insights into UPA indications and its mechanism of action.

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Introduction

Ulipristal acetate (UPA) has a licence for use as a form of emergency contraception. Over the last 6 years, this has been extended to also cover uterine fibroids (Donnez and Dolmans, 2016; Donnez et al., 2012a, 2012b; Lumsden et al., 2015; Stewart, 2015) in women with uterine fibroids associated with heavy menstrual bleeding, or with other moderate or severe symptoms (bulk symptoms, pelvic pain, decreased quality of life [QOL]).

Oral contraceptives, progestins and levonorgestrel-releasing intrauterine systems (LNG-IUS) may be used 'off label' to treat women with gynaecological bleeding disorders, but they are not indicated for management of uterine fibroids, because fibroids are progesterone-sensitive (Chabbert-Buffet et al., 2005, 2014; Kim and Sefton, 2012; Wise and Laughlin-Tommaso, 2016) (**Table 1**). Oral progestogens are reported to reduce the symptoms or prevalence by 25–50% when administered during the second half of the cycle or as a 21-day contraceptive, but there are no data on continuous administration (Sayed et al., 2011; Venkatachalam et al., 2004). The LNG-IUS device is effective at reducing menstrual blood loss and restoring haemoglobin levels and may be an alternative to surgical treatment (Sayed et al., 2011), but its effect on the size of uterine myomas is still unclear (Murat Naki et al., 2010). Studies suggest that it could be a potentially good option for symptomatic women with no endometrial distortion (Sayed et al., 2011). Combined oral contraceptives have demonstrated improvements in menstrual blood loss, but no significant change in the volume of tumours (Sayed et al., 2011). For women with menorrhagia associated with small myomas (<3 cm) causing no distortion to the uterine cavity, the National Institute for Health and Care Excellence (NICE) guideline (NG88) (2018) recommend that the following treatments may be considered: LNG-IUS, tranexamic acid, non-steroidal anti-inflammatory drugs, combined oral contraceptives or cyclic progestogens. For larger myomas or those distorting the uterine cavity and linked to menorrhagia, dysmenorrhoea or pressure symptoms, gonadotrophin-releasing hormone agonist (GnRHa) has been used to reduce myoma size and restore haemoglobin levels in symptomatic women (Donnez et al., 1989).

Table 1 – Contraindications and drug interactions.

General contraindications	Avoid UPA in patients with hypersensitivity to the substance or any of its excipients during pregnancy, breastfeeding, genital bleeding of unknown cause or for reasons other than uterine fibroids, and also in the presence of uterine, cervical, ovarian or breast cancer.
Specific contraindications	Use of UPA in women with severe asthma requiring oral glucocorticoids is not advised, as it exhibits some potential antagonist effects on glucocorticoid receptors. Use with kidney or liver disease Renal impairment is not expected to alter elimination of UPA. It is not recommended in patients with moderate and severe hepatic impairment. At the time of this manuscript, there is a review ongoing on liver parameters under UPA.
Drug interactions	SPRM are metabolized by the cytochrome P450 isoenzyme system and so drug–drug interactions may occur. Avoid co-administration of moderate (e.g. erythromycin, grapefruit juice, verapamil) or potent (e.g. ketoconazole, ritonavir, nefazodone, itraconazole, telithromycin, clarithromycin) CYP3A4 inhibitors and UPA. Concomitant use of UPA and CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone) is not advised. Both CYP3A4 inhibitors and inducers may impact plasma levels of UPA, but the clinical effects of a lower or higher dose are unlikely to provoke any clinically significant response.

SPRM = selective progesterone receptor modulator; UPA = ulipristal acetate.

What is UPA?

UPA belongs to a class of drugs called selective progesterone receptor modulators (SPRM) (Chabbert-Buffet et al., 2005). They have a direct impact on fibroids, decreasing their size, and on the endometrium, reducing excessive bleeding. They are thought to modulate progesterone pathways known to play a key role in the development of uterine fibroids (Bestel and Donnez, 2014; Bouchard, 2014; Kim and Sefton, 2012; Moravek et al., 2015; Nieman et al., 2011; Nisolle et al., 1999; Spitz, 2009). There are four members of the SPRM family of compounds: mifepristone, asoprisnil, UPA and telapristone acetate.

Molecular mechanism of action of SPRM

SPRM are synthetic compounds that exert either an agonistic or antagonistic effect on target tissues determined by their binding to progesterone receptors (Bestel and Donnez, 2014; Chabbert-Buffet et al., 2005, 2014; Kim and Sefton, 2012), their action contingent on tissue type (Bouchard and Chabbert-Buffet, 2016; Donnez et al., 2015a; Moravek et al., 2015). Their mixed activity depends on recruitment of cofactors that regulate transcription in a so-called genomic pathway, as well as non-genomic interactions with other signalling pathways (**Figure 1**). Despite a number of recent hypotheses (Whitaker et al., 2017), it is not known exactly how SPRM alleviate menstrual bleeding (Williams et al., 2012).

Mechanisms of action in the response of uterine fibroids to UPA

UPA reduces fibroid size by a combination of proliferation inhibition, transitory stimulation of apoptosis and extracellular matrix (ECM) remodelling linked to high matrix metalloproteinase-2 (MMP-2) expression levels, particularly after long-term treatment (Courtoy et al., 2015). During the early phase of treatment, apoptosis is facilitated by temporary repression of survivin, an apoptosis inhibitor (Courtoy et al., accepted) (**Figure 2**). The reduction in fibroid volume is also correlated with high MMP levels and, conversely, low tissue inhibitor of metalloproteinase (TIMP) levels, suggesting that the MMP/TIMP balance plays an important role in ECM resorption in decreasing fibroid volume (Courtoy et al., 2018). Sustained fibroid shrinkage observed even after treatment cessation might therefore be the result of permanent ECM reduction. In the context of uterine fibroids, UPA does not alter expression patterns of progesterone receptors, nor their cofactors (Courtoy et al., 2017), indicating that the molecular mechanisms involved could be more complex than presumed.

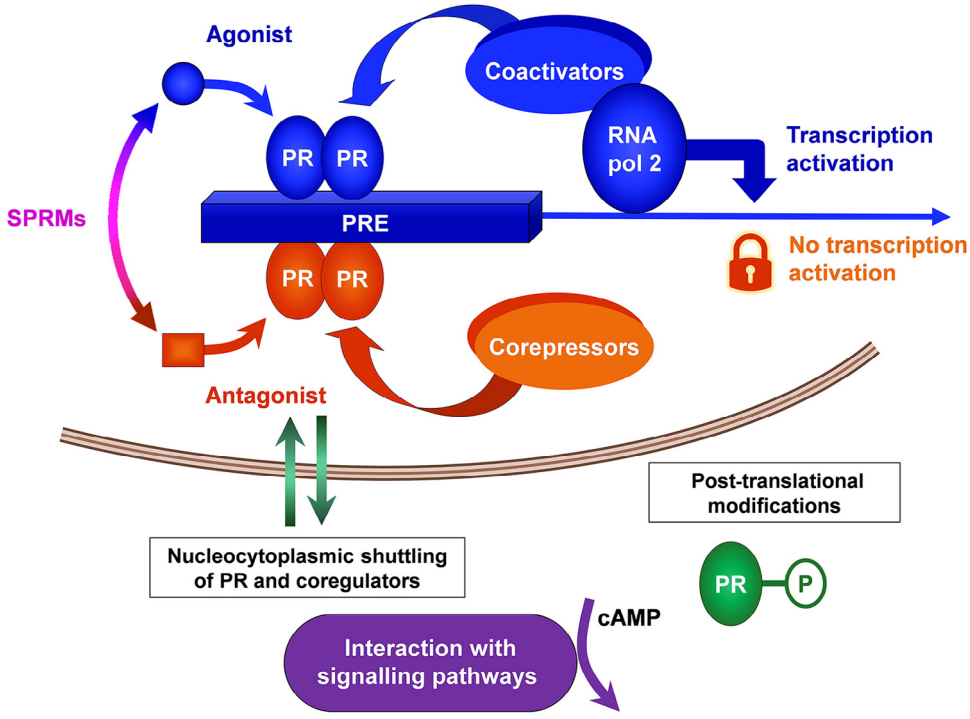

Figure 1 – Mechanism of action of selective progesterone receptor modulators (SPRM). SPRM have a direct impact on uterine fibroids, endometrium and the pituitary gland by a mechanism involving gene transcription regulation. SPRM bind to progesterone receptors (PR) with high selectivity and affinity. Once bound to SPRM, PR dimers exhibit agonist, antagonist or mixed activity. Agonist function is mediated by recruitment of coactivators in the promoting region of target genes, triggering transcription activation, while antagonist action is mediated by recruitment of corepressors that prevent transcription of target genes. Nucleocytoplasmic shuttling of PR and coregulators regulates the availability of these partners to control gene expression, and leads to non-genomic signalling in the cytoplasm (adapted from Bestel and Donnez, 2014; Chabbert-Buffet et al., 2005).

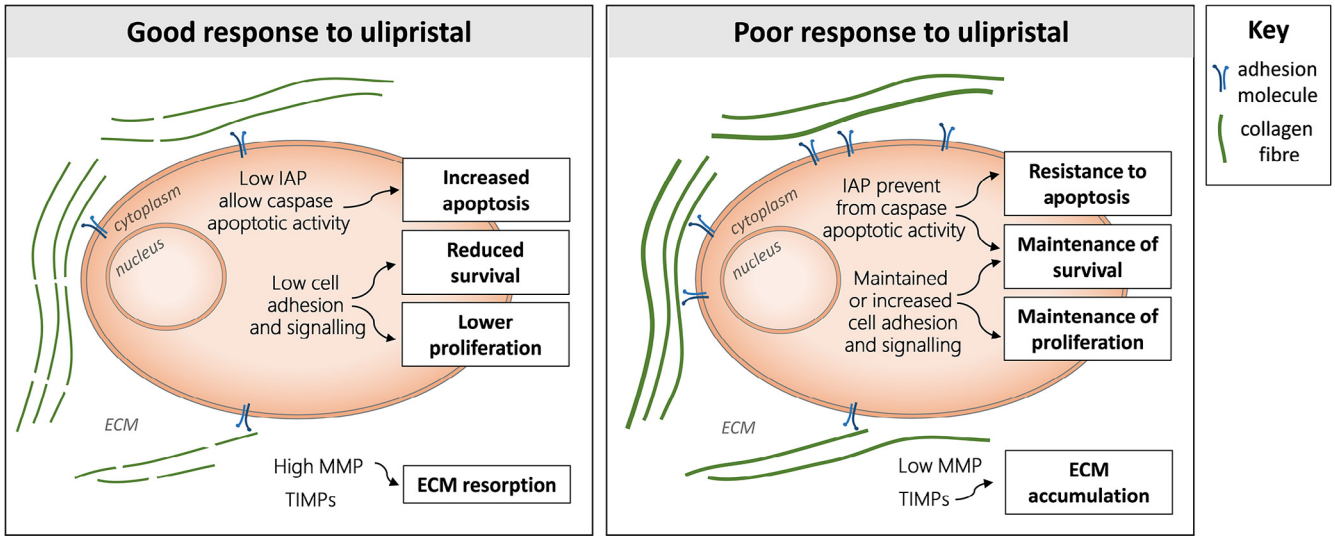

Figure 2 – Molecular response of uterine fibroids to ulipristal acetate (UPA). Distinct expression patterns reflect fibroid response (or not) to UPA. A good response is associated with lower levels of inhibitors of apoptosis (IAP), reduced cell adhesion and high matrix metalloproteinase (MMP) values, resulting in apoptosis, lower survival rates, less extensive proliferation and extracellular matrix (ECM) resorption. In case of a poor response, high IAP levels prevent apoptotic activity and ensure survival. Maintained or increased cell adhesion mediates survival and induces cell proliferation. Low MMP levels cannot resorb the collagen-rich ECM as it accumulates.

In 20% of cases, however, fibroids do not respond to UPA and their volume remains stable or they continue to grow (Donnez et al., 2015b). A poor response to UPA is associated with low MMP activity (Courtoy et al., 2018) and higher catenin delta-2 levels which, like beta-catenin, might signal toward proliferation and survival via the Wnt pathway (Courtoy et al., accepted) (**Figure 2**).

How well do SPRM work?

Mifepristone, asoprisnil, UPA and telapristone acetate have been investigated in phase II clinical trials on uterine fibroids associated with heavy menstrual bleeding. UPA has been studied in four large randomized controlled trials (RCT), which were blinded phase III clinical studies (four PEARL trials) that showed promising results in terms of both efficiency and safety (Donnez et al., 2012a, 2012b, 2014, 2015b, 2016b). Other SPRM are still under development.

Short-term use before surgery

UPA was initially approved for short-term use (3-month course) before surgery based on the first two blinded RCT (PEARL I and II), where it was compared with either a placebo or GnRHa (Donnez et al., 2012a, 2012b). The trials measured changes in blood loss, time to achieve control of bleeding, and fibroid volume reduction and regrowth at 3 months. UPA treatment looked promising (Donnez et al, 2012a, 2012b) and yielded the following findings:

(i) A significant decrease in menstrual bleeding, calculated by the pictorial blood loss assessment chart (PBAC) (Higham et al., 1990), was observed at 10 days in more than 90% of women given a 3-month course of UPA, compared with 50% in the GnRHa group at 10 days and 10% in the placebo group.
(ii) The median time needed to achieve control of bleeding was also shorter in the UPA group (5–7 days) than in the GnRHa group (30 days).
(iii) Fibroid volume decreased by around 35% after 3 months of treatment, showing a sustained effect (up to 6 months) after treatment completion.
(iv) Women treated with GnRHa experienced a 23% rate of regrowth of their fibroids at 3 months and a return to screening levels by 6 months post-treatment.

Longer-term use

UPA may facilitate surgery by shrinking fibroids, or may help avoid the need for surgery (**Table 2**). The sustained effect observed at 3 months in short-term RCT (PEARL I and II) led to further blinded RCT (PEARL III and IV) with up to four intermittent 3-month courses of UPA, including off-treatment intervals (of approximately 2 months) (Donnez et al., 2014, 2015b, 2016b). The pre-specified primary outcome of PEARL IV – the basis for licensing its longer-term use – was the percentage of women achieving amenorrhoea during the first two courses (Donnez et al., 2015b) and over all four courses combined (Donnez et al., 2016b).

The benefits and adverse effects of longer-term UPA for bleeding fibroids are presented in **Table 2**. These results show that UPA can be used to correct anaemia, as demonstrated in the PEARL I study (Donnez et al., 2012a).

As SPRM induce endometrial changes, it is recommended that UPA be prescribed in an intermittent mode (3-month therapy course followed by an interval of around 8 weeks, allowing two menstrual bleeds) to reverse any such changes. UPA should be taken at the approved daily dose of 5 mg for 3 months, as also recommended by NICE (National Institute for Health and Care Excellence [NICE] guideline [NG88], 2018) and the latest Canadian guidelines (Arendas and Leyland, 2016).

Pregnancies after UPA treatment

Information on pregnancies after UPA use is limited at present and further clinical evidence is required. In a first paper reporting a series of 18 pregnancies occurring after UPA treatment (Luyckx et al., 2014), the authors found no maternal complications related to myomas during pregnancy. All the babies were born healthy, except for one congenital abnormality not linked to the therapy. A recent paper reported a successful and uneventful pregnancy after UPA for uterine fibroids (Monleón et al., 2014). Since these two papers published in 2014, unpublished data (abstracts from data congresses, symposia) report more than 100 pregnancies after UPA use and, to date, no maternal complications and/or fetal anomalies have been detected. A recent publication (Hrgovic et al., 2018) describes a patient who conceived spontaneously while on UPA. She encountered no drug-related complications and the pregnancy resulted in the birth of a healthy baby. Furthermore, experience with UPA administered for emergency contraception reveals no additional risk of congenital anomalies (Bernard et al., 2013; Gemzell-Danielsson, 2013).

Can it be harmful?

UPA appears to have few serious side-effects. Minor adverse events are documented in **Table 2**, but these tend to diminish with repeated courses (Donnez et al., 2016a; Fauser et al., 2017). The trials monitored a number of conditions including some based on side-effects associated with UPA. Trials to date with outcomes at approximately 4 years do not show safety concerns (Fauser et al., 2017).

The safety profile of UPA during single (Donnez et al., 2012a, 2012b) and multiple (Donnez et al., 2015b, 2016a, 2016b; Fauser et al., 2017) treatment courses was well documented in the four clinical trials and no safety issues were identified from physical examination, vital signs or electrocardiograms. The most frequently encountered side-effects were hot flushes, breast pain/discomfort and headaches, but there was no increase in their incidence with repeated courses (**Table 2**). There was actually a trend towards fewer adverse effects with repeated treatment (Donnez et al., 2016b). All coagulation parameters were evaluated in detail in one of the longer-term studies (up to four courses) and found to be unchanged (Donnez et al., 2014). No cases of venous thromboembolism were reported in any of the four PEARL studies (Donnez et al., 2012a, 2012b, 2014, 2015b, 2016b). There were mild but non-significant increases in mean cholesterol and triglyceride values, but the median ratio of total cholesterol/high-density lipoprotein cholesterol remained the same (Donnez et al., 2015b, 2016b). Mean levels of liver enzymes did not change during long-term studies. Any sporadic increases were not associated with increases in bilirubin in the four PEARL studies (Donnez et al., 2012a, 2012b, 2014, 2015b, 2016b).

It is not recommended in patients with moderate and severe hepatic impairment (**Tables 1 and 3**). The European Medicines Agency (EMA) has now started a review on UPA used to treat uterine fibroids, following five reports of serious liver injury, four of which ended in liver transplants (European Medicines Agency (EMA/97889/2018), 2018). The Pharmacovigilance Risk Assessment Committee (PRAC) is evaluating all available data to determine whether there are any serious ramifications associated with use of this medication.

Table 2 – Benefits and side-effects of long-term UPA 5 mg for large fibroids associated with heavy menstrual bleeding.

UPA 5 mg

Benefits		Side effects	
• Amenorrhoea[a]			
≤1 day of spotting within 5 weeks		• Functional ovarian cyst[b]	~1%
After two courses combined	62%	• Uterine haemorrhage[b]	Uncertain, only a few reported cases
After four courses combined	49%	• Thickening of endometrial lining *(reverses when drug is stopped and menses resumes)*	
• Controlled bleeding[c]		After course 2	5%
No heavy bleeding and ≤8 days bleeding during the last 2 months of treatment		After course 4	4%
After two courses combined	81%	Symptoms	
After four courses combined	67%	• Hot flushes	
• Change in quality of life[d]		After course 2	4%
Scale from 0 (best) to 100 (worst)	*Baseline = 50 points*	After course 4	3%
After course 2	38 points better	• Breast pain/discomfort	
After course 4	34 points better	After course 2	1%
• Change in pain		After course 4	1%
Scale from 0 (none) to 100 (worst possible pain)	*Baseline = 39 points*	• Headache	
After course 2	33 points less pain	After course 2	6%
After course 4	32 points less pain	After course 4	2%
• Change in three largest fibroids			
Median change in volume from baseline			
After course 2	54% smaller		
After course 4	67% smaller		

Population: 228 premenopausal women aged 18 to 50 with moderate-to-severe symptoms of uterine fibroids (at least one fibroid >3 cm) treated with courses of UPA 5 mg/day (PEARL IV study).
The trial investigated both 5 and 10 mg doses of UPA, but 5 mg is the only dose approved by the EMA. The EMA (European Medicines Agency (EMA), 2015) and NICE (National Institute for Health and Care Excellence [NICE] guideline [NG88], 2018) have approved longer periods of use (up to four courses of 3 months each) in a broader population of women with fibroids and heavy menstrual bleeding not scheduled for surgery, based on the results of the PEARL IV study (Donnez et al., 2015b, 2016b). Use of UPA is not yet approved by the US Food and Drug Administration (FDA).
EMA = European Medicines Agency; SPRM = selective progesterone receptor modulator; UPA = ulipristal acetate.
[a] Primary efficacy endpoint: percentage of subjects in amenorrhoea at the end of all four treatment courses, where amenorrhoea was classified as no more than 1 day of spotting in a 35-day period (Donnez et al., 2016b).
[b] Source: Esmya Summary of Product Characteristics. Information concerning the ovarian cyst and uterine haemorrhage comes from the product information.
[c] Secondary efficacy endpoint: amenorrhoea at the end of each individual treatment course (1, 2, 3 and 4); controlled bleeding in the last 56 days of each individual treatment course (defined as no episodes of heavy bleeding and a maximum of 8 days of bleeding during the last 56 days of a treatment course); time to amenorrhoea during treatment courses 1, 2, 3 and 4; volume of three largest fibroids; and pain and quality of life (Donnez et al., 2016b).
[d] Measured by the uterine fibroid symptom quality of life (UFS-QOL) severity score.

Bone mineral density

In one study (PEARL II) (Donnez et al., 2012b), bone marker evaluation showed that UPA did not alter bone mineral density, unlike GnRHa, which lowers it. This may be explained because oestradiol values remain at the level of the mid-follicular phase during UPA therapy, while under GnRHa, oestradiol values are post-menopausal.

Endometrial changes

SPRM induce formation of large cystic glands in the endometrium and changes within the stromal compartment, including fibroblasts and the vasculature (Donnez et al., 2014, 2015b; Mutter et al., 2008). In the available trials, the changes remained benign and present in almost 70% of patients during treatment (Donnez et al., 2012a, 2012b, 2014, 2015b, 2016a, 2016b; Williams et al., 2012). Cystic and stromal changes appear to be reversible and benign, as their prevalence returned to screening levels (±10%) 2 months after the end of therapy in all PEARL studies (Donnez et al., 2014, 2015b, 2016a, 2016b). Moreover, in a very recent study, the extended PEARL III trial, neither atypical hyperplasia nor endometrial adenocarcinoma were reported in women undergoing eight courses of UPA treatment (Fauser et al., 2017). An approach to monitoring patients on SPRM is suggested in **Table 3**.

Table 3 – A suggested approach to monitoring patients on SPRM.

Before starting treatment, offer patients:	A vaginal ultrasound in the post-menstrual period to check endometrial thickness and for the absence of polypoid structures, and to evaluate the number and size of myomas. Haemoglobin measurement to assess the degree of anaemia and liver function tests (transaminases) to rule out liver disease. Endometrial biopsy and/or hysteroscopy in women with abnormal bleeding (intermenstrual bleeding).
Arrange follow-up after two courses of 3 months to:	Repeat the vaginal ultrasound to evaluate myoma size. Undertake further investigation of the uterine cavity if intermenstrual bleeding persists for more than 3 months after stopping treatment.

SPRM = selective progesterone receptor modulator.

Table 4 – Comparison of different therapies for the management of uterine fibroids.

Therapy	Advantages	Disadvantages
Oral contraceptives	Oral administration	No reduction in fibroid size Inconsistent bleeding
Progestin	Oral administration	No reduction in fibroid size Inconsistent bleeding
Levonorgestrel-releasing IUD	Prolonged effect Concomitant contraception	No reduction in fibroid size Spontaneous expulsion of the device Contraindicated in the presence of submucous fibroids
GnRHa	Sustained release (1 month) Fibroid volume reduction Indicated for fibroids	Injectable therapy Fibroid regrowth upon treatment cessation Temporary treatment (max. 6 months) due to adverse events (menopausal symptoms, bone mineral density loss)
UPA	Oral administration Fast bleeding control Sustained fibroid volume reduction Indicated for fibroids	Progesterone receptor modulator associated endometrial changes)

GnRHa = gonadotrophin-releasing hormone analogue; UPA = ulipristal acetate.

How cost-effective is UPA?

There are no cost-effectiveness analyses on UPA as a bridge to surgery in the short or longer term. Future research is looking to identify whether UPA is both clinically efficient and cost-effective as an alternative to surgery (Maratea, 2016).

In France, the use of UPA in women eligible for surgical procedures for uterine fibroids between 2013 and 2015 was associated with cost savings estimated at €13.6 million. This was the result of both preoperative and intermittent indications by decreasing the need to perform surgeries (Fernandez et al., 2017).

The scale and cost of heavy menstrual bleeding caused by fibroids is hard to quantify precisely.

How do SPRM compare with other treatments?

Oral contraceptives, progestins and LNG-IUS may be used 'off label' to treat women with gynaecological bleeding disorders, but they are not indicated for management of uterine fibroids, as fibroids are progesterone-sensitive (Wise and Laughlin-Tommaso, 2016) (**Table 4**). Moreover, LNG-IUS are contraindicated in case of fibroids that distort the uterine cavity (Bayer, 2018). GnRHa cannot be used for more than 3–6 months at a time, as it has side-effects (like hot flushes and vaginal dryness) and may reduce bone mineral density. Control of bleeding is achieved faster with UPA than with GnRHa and, importantly, UPA delivers a sustained effect, while rapid fibroid regrowth is observed after completion of GnRHa therapy (Donnez et al., 2012b).

Conclusions

SPRM, like UPA, are beneficial in the management of uterine fibroids, as they are able to control bleeding and reduce fibroid size. UPA therapy should be based on a patient's age and their desire to preserve fertility or avoid surgery such as myomectomy or hysterectomy. As SPRM induce endometrial changes, it is recommended that UPA be prescribed in an intermittent mode. The most frequent adverse events are headaches, hot flushes and breast tenderness, but their incidence remains low and declines with subsequent treatments. Conferred and specific contraindications should be nevertheless taken into account.

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