

SOGC Clinical Expert Opinion in response to European Medicines Agency recommended revocation of Ulipristal Acetate

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Thank you for the opportunity to contribute an expert clinical opinion into your examinations of the safe use of Ulipristal Acetate in the management of uterine fibroids. To address the questions that you posed, we assembled a panel of experts, who are both deeply knowledgeable of the scientific literature, but who also care for substantial numbers of women with uterine fibroids and have that knowledge of the impact on women's health, the options available for treatment as well as the considerations women bring to the discussion of an informed choice.

Any consideration of the role of the selective progesterone receptor modulator (SPRM), ulipristal acetate (UPA), in the Canadian clinical armamentarium has to be taken with an understanding of the impact of uterine fibroids on women's health. Uterine fibroids are the most common benign pelvic tumor in women, and are found in up to 68% of women, although not all are symptomatic. The symptoms range from pain and heavy menstrual bleeding to impacts from compression by the mass on bladder bowel and large veins.

Women with symptomatic fibroids experience diminished quality of life, reduction in the ability to participate in usual activities, loss of time from work, sexual dysfunction and reduced fertility. Uterine fibroids do not impact all women to the same extent. They disproportionately affect the health of black women, with both greater severity and a younger age, leading to a greater impact on the health of women of child-bearing age. In a recent U.S. study¹ nearly one third of women who had undergone a hysterectomy for symptomatic fibroids would have been interested in non-surgical management; in 46% of those it was to have preserved child bearing capability. This is all the more true for the many more women who do not undergo hysterectomy.

The decision to proceed to a hysterectomy for a benign tumor is a decision in which a woman's preference and choices are paramount. It will be determined by her values, as well as by the health impairment she is experiencing, the acceptability of the competing risks and benefits of the options provided, and health goals that she holds. All options carry risks, for every woman the answer will be unique to her.

Because uterine fibroids are benign, it is reasonable to have a very high standard of safety for any therapy, but the reality is that for women with fibroids all options, including taking no action, carry risks. With this context, the panel addressed the questions you posed.

Question 1:

a) What would be the impact, in clinical practice, of the removal of the pre-operative treatment indication for ulipristal acetate?

Removal of UPA would remove an important tool in the management of women with heavy menstrual bleeding in association with uterine fibroids.

- UPA uses a novel mechanism for effectively managing abnormal uterine bleeding, that addresses the cause of the bleeding, as opposed to managing the symptoms.
- HMB is one of the most common and problematic issues seen in gynecology clinics, and the associated iron deficiency anemia is increasingly understood to contribute to impaired health.
- Preoperative anemia (a quality metric) is a very important patient safety issue and up to a quarter of women undergoing GYN surgery (especially those with fibroids) are known to be anemic prep. SPRMs give gynecologists an option to improve hemoglobin and correct preoperative anemia – studies have consistently shown that this medication is effective.
- Use of UPA reduce need for urgent care, blood transfusions and optimizes blood count. These are benefits in and of themselves, and offer additional benefits in the pre-operative context.
- Optimizing blood counts pre-operatively surgical risks of transfusion or infection and improves recovery time.
- Side effects are fewer (and more tolerable) than comparator medication (GnRH agonist)
- Tablet is preferred to injections by patients

b) What would be the impact, in clinical practice, of the removal of the intermittent treatment indication for ulipristal acetate for patients not eligible for surgery/ hysterectomy?

- One of our first line choices for managing symptomatic uterine fibroids because of its direct effect on fibroid without the side effects seen with other choices (ex. GnRH agonist)
- Removes a very valuable part of our choices for these patients who are unable to take other options due to other risk factors
 - Example: patients who have an underlying DVT risk with birth control pill can take UPA; patients who are not able to tolerate progestins due to mood side effects
- Improves blood count, reduces need for transfusion
- Medically few true contraindications, few drug reactions
 - Especially important in patients who are not eligible for surgery since they often have other comorbidities

c) What would be the impact, in clinical practice, of the removal of ulipristal acetate from the market?

Current challenges with surgery:

- The wait times for elective gynecologic surgery are very long- they a concern prior to COVID, and are markedly worse now. UPA controls blood loss and offers symptomatic benefit while the patient waits
- Risk of surgery is real, and the complications are serious (risk of transfusion, injury to the uterus and other organs)
- Surgical management, particularly of large fibroids, or after prior surgery, or where fibroids and endometriosis co-exist, frequently requires referral to tertiary centers, further prolonging wait times.
- Women who have not completed child bearing do not want to lose their uterus, nor do they wish to be on medications that induce a chemical menopause.
- Alternative medical options like GnRH agonists have their own side effects. All side effects are less with UPA than the alternatives available
- Hypo-estrogenism, with menopausal symptoms and the risks of prolonged hypo estrogenism;
- Bone loss, with >6 months' use
- Mood changes

- Risks of oral contraceptives, particularly with large fibroids that can cause venous stasis.

As gynecologists, our goal is to improve the quality of life of our patients, many of whom are seriously affected with fibroids. SPRMs are effective in improving quality of life, objectively measured. Restricting or removing this option for patients would really limit our ability to help our patients.

Question 2: What is the feasibility, in clinical practice, of defining a patient population that is not eligible for hysterectomy or surgery and for which ulipristal acetate would be the only treatment option for moderate to severe symptoms of uterine fibroids? How would this selection of patients be done in clinical practice?

- It is a straightforward but thorough assessment that balances patient choice, patient concomitant health issues and availability of acceptable options in the patient's region
- Patient choice is very important in this area of care. Many patients do decline major surgery such as hysterectomy to manage their symptomatic uterine fibroids. Women know options, and exercise their right of informed choice and consent. The exclusion of surgery as an option is frequently patient, not provider driven.

Question 3:

a) How do the experts see the benefits of ulipristal acetate 5 mg beyond symptom relief, i.e. avoiding surgery/hysterectomy in the longer term?

- Avoiding surgery is a very important benefit since surgery for uterine preservation procedures is associated with a high recurrence risk (30%) and where the second surgery is more difficult than the first
- Other complications of surgery like hysterectomy long term are a real burden on our society
 - Ex. incontinence, uterine prolapse, bowel adhesion, chronic pain

b) In your clinical experience, does pre-operative treatment with ulipristal acetate facilitate a less extensive surgical procedure such as hysteroscopic myomectomy, and if so, to which extent?

- Improves preoperative hemoglobin to allow for better surgical recovery
 - Rapid bleeding response
 - Convenience of oral agent (comparator GnRH agonist is an injection by a HCP)
 - Non-anemic patients have decreased complications up to 30 days postoperatively.
- UPA helps to shrink fibroids in some cases and that further helps with surgical approach to a less invasive approach

Question 4: How do experts see the risks associated with ulipristal acetate 5 mg compared to the risks associated with hysterectomy/surgery procedure and how could these be best communicated to the patient?

- The risks are very personalized and should be assessed case by case
- The risks of surgery are well documented and are higher than the risks attached to UPA. In certain patients, the risk is much higher for surgery (example injury in those with multiple previous surgeries and scarring is significant, risk of those who are medically compromised)

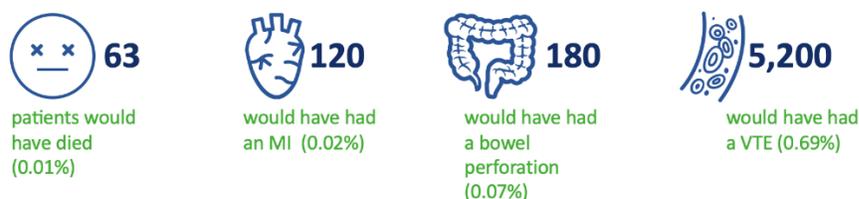
Communication of risks in general, and very rare risks in particular, is complex.

- We do not perceive risks uniformly. We tend to perceive risks as greater if we are anxious, compared to when we are calm. We will be influenced in risk perception by recent experience. We tend to

attribute greater relevance to new risks, to new medications, compared to a familiar one, e.g. acetaminophen or the oral contraceptive. We are more aware of risks if they have received media or social media attention, and we are more intolerant of risks if they are for a condition that we may regard as not a serious. Fibroids and heavy menstrual bleeding may be seen as inconveniences, rather than the medical problems that they are.

- These problems are compounded when dealing with rare or very rare risks. According to the WHO, a frequency of < 1: 10,000 is very rare. A risk of < than 1:100,000 is very hard for us to comprehend. To communicate these risks, it is important to use relevant comparators, or graphic illustrations to help make the risks tangible. The infographic below² is an example of a risk communication tool. Check lists for providers and patients can also help guide a risk discussion.

If 765,000 patients had undergone Laparoscopic hysterectomy approximately:



Note: no data on Myomectomy but this procedure is not without risks

- Risk discussions should be informed by evidence based guidelines, such as the SOGC Clinical Practice Guidelines, and can be augmented by evidence based patient information in written or web based formats. A well informed decision takes sufficient time to digest information that can at first seem overwhelming.

Women who choose treatment with UPA, must agree that they have a responsibility to undertake regular liver function testing, and to report any symptoms that are suggestive of hepatic involvement. Any facilitation of adherence to testing should improve safety.

The experts convened for this opinion were unanimous in their opinion that UPA does offer an important and safe tool for the management of symptomatic fibroids, and that it can be given safely, informing women of all relevant risks, and respecting choice and autonomy.