CADTH

CADTH COMMON DRUG REVIEW

Request for Advice

ULIPRISTAL ACETATE (FIBRISTAL)

(Allergan Inc.)

Indication:

- Preoperative treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age.
- Intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

The duration of each treatment course is three months.

Service Line:	CADTH Common Drug Review
Version:	Final (with redactions)
Publication Date:	August 2019
Report Length:	26 Pages

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Abbreviations

CANFib	Canadian Women with Fibroids
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
GnRH	gonadotropin-releasing hormone
HRQL	health-related quality of life
PBAC	Pictorial Blood Loss Assessment Chart
QALY	quality-adjusted life-year
RCT	randomized controlled trial
UFS-QoL	uterine fibroids symptoms and health-related quality of life

Drug	Ulipristal acetate (Fibristal)
Indication	Fibristal (ulipristal acetate) is indicated for: • preoperative treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age • intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery. The duration of each treatment course is three months.
Request for Advice Questions	The current Health Canada indication for Fibristal is a revised indication from the following previous indication: Fibristal (ulipristal acetate) is indicated for: • Treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age, who are eligible for surgery. • Intermittent treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age. The duration of each treatment course is 3 months. Given that the CADTH Canadian Drug Expert Committee has issued a recommendation for Fibristal in November 2017 based on the previous Health Canada indication, should the CDEC recommendation for ulipristal acetate (Fibristal) be updated or revised to address the changes in the product monograph?
Dosage Form(s)	Tablet, 5 mg
Date of Product Monograph Revision	December 19, 2018
Manufacturer	Allergan Inc.

Background

The Recommendation, Reasons for the Recommendation, and Of Note sections in the November 2017 CADTH Canadian Drug Expert Committee (CDEC) recommendation for ulipristal acetate for treatment of uterine fibroids state the following:

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ulipristal acetate be reimbursed for the treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery, and the intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age, with the duration of each treatment course being three months, if the following conditions are met:

Conditions:

- The patient is under the care of an obstetrician/gynecologist.
- Treatment should be limited to a maximum of four courses of therapy.

Reason(s) for Recommendation

1. In two trials reviewed in the original submission of ulipristal acetate for the treatment of uterine fibroids (PEARL I and PEARL II), one three-month treatment course of ulipristal acetate was shown to be superior to placebo and noninferior to leuprolide acetate for decreasing menstrual bleeding in patients with uterine fibroids.
2. Results from one double-blind, multi-centre, randomized, dose-controlled trial (PEARL IV; N = 451) in premenopausal women with uterine fibroids indicated that, after four courses of treatment with ulipristal acetate, 49% of patients achieved amenorrhea. Patients also experienced a reduction in Pictorial Blood Loss Assessment Chart score and a reduction in median fibroid size from baseline. No major safety concerns were reported in PEARL IV, and the safety profile was similar to what was reported in the PEARL I and PEARL II trials.
3. The efficacy and safety of ulipristal acetate beyond four courses of treatment is uncertain.

Of Note

- CDEC noted that the drug plan costs for ulipristal acetate when used as a treatment based on the original indication (i.e., as a treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery, for a duration of three months, with treatment limited to one course of therapy) should still not exceed the drug plan costs for the manufacturer's identified comparator, leuprolide acetate, as specified in the original CDEC recommendation.
- CDEC noted that, based on the updated indication for ulipristal acetate, the CADTH Common Drug Review (CDR) reanalysis found six months of treatment with leuprolide acetate, followed by abdominal hysterectomy, to be more effective but costlier than four courses of ulipristal acetate, with an incremental cost per quality-adjusted life-year (QALY) gained of $25,158. This value of the incremental cost per QALY gained is within a range that is normally considered by CDEC to reflect cost-effective treatment options, which suggests that treatment with leuprolide acetate prior to hysterectomy is the optimal therapeutic choice. However, the manufacturer did not include any utility benefit from avoiding hysterectomy for women who wish to preserve their uterus. As this is an option that many patients would prefer compared with undergoing surgery (based on input from patient groups and the clinical expert consulted for this review), the inclusion of such a utility benefit would have decreased the cost-effectiveness of treatment with six months of leuprolide acetate prior to hysterectomy. When combined with uncertainty around the cost-effectiveness estimate for the treatment with leuprolide acetate, failure to consider any potential utility benefits because of the avoidance of surgery increases the likelihood that the incremental cost per QALY gained of treatment with six months of leuprolide acetate prior to hysterectomy will exceed $25,000. Therefore, it is unclear whether six months of treatment with leuprolide acetate prior to hysterectomy is a more cost-effective option compared with four courses of ulipristal acetate. The committee also recognized that four courses of ulipristal acetate should have been compared with a wider range of treatment options (e.g., abdominal hysterectomy or embolization) in the cost-effectiveness analysis. However, additional economic analyses were limited because of the lack of comparative clinical information and, as such, the economic impact of the use of ulipristal acetate on the health care system remains uncertain.

The primary conclusions for the November 2017 Request for Advice clinical review were, as follows:

"In November 2013, CADTH issued a CDEC recommendation that ulipristal acetate (Fibristal) be listed for the treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age, who are eligible for surgery, if the following conditions are met: 1. The duration of treatment with ulipristal acetate should not exceed three months. 2. The patient is under the care of an obstetrician/gynecologist. 3. The drug plan costs for ulipristal acetate should not exceed the drug plan costs for the manufacturer's identified comparator, leuprolide acetate. Since this recommendation was issued, both the indication and the number of eligible treatment courses for ulipristal acetate have been revised, no longer restricting the patient population to those eligible for surgery and no longer restricting treatment to one three-month treatment course. A request for advice was received from the CDR-participating drug plans to CADTH to ask if the CDEC recommendation for ulipristal acetate (Fibristal) from 2013 should be updated to address the revised indication and eligible treatment courses.

"One double-blind, multi-center, randomized, dose-controlled trial (PEARL IV; N = 451) in premenopausal women with uterine fibroids between 3 cm and 12 cm inclusively, heavy menstrual bleeding of greater than 100 (Pictorial Blood Loss Assessment Chart [PBAC]), and uterine size of less than16 weeks of gestation met the inclusion criteria of the review. Patients were randomized into four treatment courses of 5 mg or 10 mg ulipristal acetate once daily, with each treatment course lasting for three months, between which patients were off-treatment. The CADTH CDR review focused on the results of the 5 mg treatment group, as this aligns with the Health Canada–approved indication. The efficacy results from PEARL IV indicated that 48.7% (95 out of 195) of patients achieved amenorrhea after four treatments (95/195 [48.7%]), patients experienced a reduction in the PBAC score from a mean of 300 at baseline down to a mean of 139.7 and a 67% reduction in median fibroid size from baseline. No major safety signals were reported in PEARL IV and the safety profile was similar to what has been reported in PEARL I and II, and, according to the clinical expert, similar to what has already been seen in clinical practice. The results of the PEARL IV trial were limited by the lack of a comparator group and the lack of long-term efficacy and safety outcomes beyond four courses of treatment.

"In the absence of direct comparative evidence, the manufacturer submitted an indirect comparison (IDC) that was based on the extrapolation of the comparative efficacy results from PEARL I and II to subsequent treatment courses (course 2, 3, and 4). A Bayesian network meta-analysis (NMA) using the extrapolated data w used to provide indirect comparative evidence of the efficacy of ulipristal acetate 5 mg over multiple courses. 4 The resulting outcomes of such analysis were highly uncertain and cannot be used to inform on the potential comparative efficacy of ulipristal acetate.

"Based on the CADTH reanalysis of the manufacturer-submitted economic model, intermittent treatment with ulipristal acetate (four courses) was both less effective and less costly than six months of treatment with leuprolide acetate followed by abdominal hysterectomy. The incremental cost per quality-adjusted life-year (QALY) gained for six months of treatment with leuprolide followed by abdominal hysterectomy compared with an intermittent treatment with ulipristal acetate (four courses) was $25,158 per QALY. The inflexibility of the submitted model, the lack of comparative data, and the lack of long-term data on the need for hysterectomy results in a CADTH reanalysis that remains speculative."

Request for Advice

The CDR-participating drug plans have submitted a request for advice (RfA) to CADTH regarding the 2017 recommendation for ulipristal acetate (Fibristal) for the treatment of uterine fibroids. In November 2017, CADTH issued a CDEC recommendation that ulipristal acetate (Fibristal) be reimbursed for the treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery, and for the intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age, with the duration of each treatment course being three months, if the following conditions are met:

- The patient is under the care of an obstetrician/gynecologist.
- Treatment should be limited to a maximum of four courses of therapy.

Since this recommendation was issued, Health Canada has conducted a safety review for ulipristal acetate regarding reports of serious liver injury; the safety review found a possible link between ulipristal acetate and the risk of liver injury.[1] Consequently, Health Canada worked with the manufacturer of ulipristal acetate to update the product safety information. Ulipristal acetate is now contraindicated for women who currently have or previously had liver problems. Women for whom the drug is to be prescribed are required to have liver functions monitored before, during, and after treatment. In addition, Health Canada has restricted the intermittent use of the drug to women of childbearing age who are not eligible for surgery.[2] Table 1 provides an outline of the previous and updated indications.

Table 1: Previous and Revised Health Canada Indications

2017 Indication	Fibristal (ulipristal acetate) is indicated for: • the treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery • the intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age. The duration of each treatment course is three months.
Revised Indication	Fibristal (ulipristal acetate) is indicated for: • The preoperative treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age. • The intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery. The duration of each treatment course is three months.

The CDR-participating drug jurisdictions are requesting that CDEC provide advice regarding the following:

- Should the CDEC recommendation for ulipristal acetate (Fibristal) be updated or revised to address the changes in the product monograph?

CDR Approach to the Request for Advice

In order to address the RfA questions, the CDR review team updated the systematic review in the 2017 Request for Advice Clinical Report.

Randomized controlled trials (RCTs) were selected for inclusion based on the selection criteria defined and presented in an updated predefined protocol. The detailed review methodology and protocol is presented in Appendix 1. A clinical expert with experience in the treatment of women with uterine fibroids was consulted by the review team to provide input on the interpretation of findings and the potential place in therapy of ulipristal acetate.

Findings

A total of 291 reports were identified from the literature for inclusion in the updated systematic search. No study was found to match the inclusion and exclusion criteria described in here. The aim of this clinical review will be to provide information regarding the recent Health Canada safety review, the practice implications of the Health Canada–revised product monograph as described by the clinical expert consulted by CADTH, and to summarize the patient input received for this RfA.

Health Canada Review of Ulipristal Acetate Safety Risk

On March 15, 2018, Health Canada announced that a safety review of ulipristal acetate would be conducted as a result of Canadian and European reports of serious liver-related adverse events. These reports included serious liver impairments that required liver implants. At the time, Health Canada communicated the need to monitor liver functions in women who are prescribed ulipristal acetate.[3]

On September 7, 2018, Health Canada published a summary of the safety review. The summery outlined that, in 2017, there were more than 63,000 filled prescriptions of ulipristal acetate in Canada. Health Canada reviewed 31 reports (seven Canadian and 24 international) of serious liver injury with the use of ulipristal acetate and found that a link may have existed in 20 cases. Beyond these reported cases, Health Canada conducted a review of existing published literature; the review of published literature did not identify any observations of a possible link between the use of ulipristal acetate and liver injury.[1]

Health Canada's review concluded that there may be a link between the use of ulipristal acetate and liver injury. Consequently, Health Canada worked with the manufacturer of ulipristal acetate to update the product safety information. Ulipristal acetate is now contraindicated for women currently with or have previously had liver problems. Women for whom the drug is to be prescribed are required to have liver functions monitored before, during, and after treatment. In addition, Health Canada restricted the intermittent use of the drug to women of childbearing age who are not eligible for surgery.[2]

Place in Therapy[a]

Uterine fibroids tend to affect women of reproductive age.[4,5] Women with symptomatic uterine fibroids often experience heavy menstrual bleeding, pelvic pressure, and pain.[4,5] The choice of treatment for symptomatic fibroids is influenced by the symptom profile, the desire

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

for future childbearing, the desire to retain uterus, menopausal status, and patient preference.[4] In cases where treatment is being considered, the benefits of symptom relief are balanced against the potential risks of therapy.

Conventional treatment options for uterine fibroids have generally been invasive, including hysterectomy, myomectomy, and uterine artery embolization.[4] Gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide acetate) may be used preoperatively to decrease the size of fibroids and increase a patient's hemoglobin, but GnRH is not used for long-term treatment because of concerns regarding loss of bone mineral density. For women who wish to preserve their childbearing potential, the treatment options have traditionally been limited to myomectomy.[4]

Myomectomy is often presented as an alternative to hysterectomy for women with symptomatic fibroids. However, myomectomy carries greater surgical risk than hysterectomy because of a higher risk of blood loss and the need for transfusion. Myomectomy may also compromise the integrity of the uterus and cause pelvic adhesions. Also, fibroids have an approximately 15% to 50% recurrence rate in women who have undergone myomectomy.[4] Further, for women with subserosal and intramural fibroids, the evidence does not support the removal of fibroids for fertility.[5]

Uterine artery embolization has been investigated as an option for these women. However, it is associated lower pregnancy rates, higher miscarriage rates, and more adverse pregnancy outcomes compared with myomectomy. Studies also suggest that uterine artery embolization is associated with a loss of ovarian reserve.[5] As such, uterine artery embolization has limited utility in the treatment of women who wish to retain their uterus for childbearing.

The **long-term use of GnRH agonist** (e.g., leuprolide acetate) is generally not a treatment option for fibroids because of the resulting side effects that include the presence of menopausal symptoms and concerns regarding the loss of bone mineral density.[4]

For women with symptomatic fibroids and a desire for uterine preservation and the avoidance of risks associated with myomectomy, the **long-term use of ulipristal acetate** may be considered a viable treatment option that does not carry the risks associated with aforementioned more invasive options. While initially investigated among women awaiting surgery,[6,7]more recent studies on the long-term use of ulipristal acetate have reported the efficacy and safety of four repeated 12-week treatment courses of daily 5 mg or 10 mg ulipristal acetate.[8,9] These studies have provided the rationale for the long-term use of ulipristal acetate beyond the four courses currently reported in the literature. Patients who experience amenorrhea with this medication will generally become amenorrheic within two courses of treatment.[8] In women whose bleeding symptoms are not responsive to this medication after two courses, only a small incremental benefit is seen with further treatment.[8]

As all surgery is associated with surgical risk, medical options — if safe and effective — are generally preferred to surgical options. However, despite the availability of non-surgical options for the treatment of uterine fibroids, their use may be limited by contraindications, the desire for childbearing, or the lack of effectiveness of treatment in certain women. For these reasons, surgery — and in particular hysterectomy — remains the most effective treatment for uterine fibroids. As surgery is the most effective treatment for uterine fibroids, women with symptomatic uterine fibroids who are not candidates for non-surgical treatment or who have not responded to medical management should be provided with access to

surgical options. In cases where women are at elevated surgical risk because of baseline comorbidities, the risks of surgery need to be balanced against debilitation and the negative health effects of symptomatic uterine fibroids.

Patient Input Summary

This section was summarized by CADTH staff based on the input provided by patient groups.

Brief Description of Patient Group(s) Supplying Input

One patient group provided input on this review — CANFib, Canadian Women with Fibroids. CANFib provides research and data to physicians, pharmaceutical firms, and government to help advance the treatments of fibroids and endometriosis.

The patient input submission from CANFib was prepared by internal staff. CANFib received financial payment over the past two years in the range of $5,001 to $10,000 from Allergan, Inc. and Bayer AG.

To prepare the patient input, CANFib used information derived from a combination of a survey performed in December 2019 together with aggregate data extracted from discussion groups based on keyword tags and accumulated responses that were subsequently slotted into groups designed to fit survey criteria. A total group of 343 women were involved in the information gathered for the patient input.

Condition-Related Information

CANFib describes that, when patients joins the group, they have reached a point were symptoms related to their fibroids are unacceptable. The group reports that patients adopt strategies to hide the bleeding caused by fibroids, including wearing black track pants, knowing in advance where public washrooms are, or simply avoiding leaving the house. Patients also indicate painful periods and/or pain between periods and excess bleeding that may lead to days off work or blood transfusions. Many of these symptoms cause embarrassment, where patients may need to change their clothing, chairs, or mattresses due to excessive blood stains. Patients face depression, weakness, pain, and isolation.

Current Therapy-Related Information

Few treatments outside of the surgical spectrum are available for patients suffering from fibroids. Commonly used medications include birth control, the Mirena IUD, ibuprofen, a Lupron Injection, and Fibristal. Patient experience indicates that birth control often works well for a period of time before losing efficiency in controlling the symptoms, Lupron is usually avoided due to side effects, and that ibuprofen is useful but not sufficient to relief symptoms. Women who have used, or contemplated using, Fibristal did so either to try and avoid surgery completely or to give themselves more time before taking the surgical option.

Improved Outcomes

Surveyed women indicate that they prefer a non-surgical and non-hormonal option to discontinue, or significantly reduce, bleeding. An optimal treatment would allow women to continue their life and work uninterrupted; avoid loss of income, blood transfusions, and other risky procedures; and avoid having to take additional medication. In addition, women

who were considering the surgical option wanted time to consider the surgical option, and wanted time to build strength and blood stores beforehand.

Expectations About the Drug Being Reviewed

Of the surveyed women, 343 had experience with Fibristal. Of these, 315 reported being satisfied with the medication, whereas 28 found the side effects difficult during the first month; and of those, 21 found month two (and onward) acceptable while seven discontinued its use for that reason. One patient chose to discontinue using Fibristal because of elevated liver enzymes, citing that she wished to continue taking iron and painkillers instead.

Surveyed women were well aware of the Health Canada safety review. Their main fear is that a drug that has worked for them might be taken away. Women who responded that their experience with Fibristal was successful, either immediately or within two months of treatment, reported being able to enjoy a lifestyle similar to the one they enjoyed before having fibroids.

Discussion

As a consequence of Health Canada's safety review of ulipristal acetate, several changes were applied to the product monograph of Fibristal. Most notably is the additional contraindication for its use in patients with a current or previous history of liver disease.[10] In addition, Health Canada has restricted the intermittent use of ulipristal acetate to patients who are not eligible for surgery.[10] The CADTH clinical review team has worked closely with the clinical expert consulted on this RfA to try and determine what constitutes a patient not being eligible for surgery. The clinical expert clarified that there is no specific fibroid-related clinical presentation that would make a patient not eligible for surgery. The clinical expert elaborated that patients fall into a surgical risk spectrum based on their overall health, respiratory health, blood work, weight, and other factors; the surgical decision-making process weighs the benefits to the risks in any given patient. In addition, the clinical expert emphasized that a patient's choice plays a major role in the decision to undergo surgery or not, and that treatment options for patients who decide not to go through surgery, regardless of the reason, are limited. In essence, the clinical expert explained that patients may be not eligible for surgery because of personal choice rather than because of a clear medical reason.

The clinical expert also related to the clinical team that Health Canada's safety review has had an impact and that it has initiated discussions among gynecologists: The revisions to the product monograph have led to changes in practice, where screening and monitoring liver functions are now a standard practice for patients who are prescribed ulipristal acetate.

There is no new evidence of clinical efficacy from RCTs of ulipristal acetate for the treatment of fibroid tumours. CDEC's previous recommendation was based on the PEARL IV study, where the study does not explicitly assess the risk for surgery in the enrolled patients.[9]

Conclusions

Health Canada's safety review based on several reports of liver injury led to revisions in the ulipristal acetate product monograph, where it is now contraindicated for use in patients with a current or previous history of liver disease. Monitoring liver functions is now considered essential for patients receiving the drug. In addition, Health Canada has restricted the intermittent use of Fibristal to patients who are not eligible for surgery.

No new clinical evidence for efficacy form RCTs has been identified. In addition, no clear definition exists for patients with fibroid tumours who are not eligible for surgery. The clinical expert consulted on this review explained that a patient's choice plays a major role in deciding treatment approach, including undergoing surgery. The clinical expert also elaborated that patients fall into a spectrum of surgical risk and if a surgery would lead to benefits that outweigh the surgical risk then surgery would be attempted.

As such, in the absence of a clear consensus regarding what defines a patient population not being eligible for fibroid surgery (either due to purely medical reasons or due to choice), and in the absence of new clinical efficacy evidence beyond what was presented in the last clinical review of ulipristal acetate, no clear inference can be made regarding the consequence of the changes in the wording of the indication in product monograph. Beyond the changes in the wording of the indication, Health Canada has clearly communicated that ulipristal acetate is contraindicated in patients with a current or a history of liver disease and that patients who are prescribed ulipristal acetate must have their liver functions monitored before, during, and after treatment with ulipristal acetate.

Appendix 1: Methodology

Objectives

To update the 2017 systematic review of the beneficial and harmful effects of the intermittent use of ulipristal acetate 5 mg for the treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age.

Literature Search Methods

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[11]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Fibristal (ulipristal acetate). Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was limited to documents published between January 1, 2016 and April 29, 2019 but was not limited by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

This report makes use of a literature search conducted in June 2017 for a previous request for advice (RfA) Fibristal CADTH Common Drug Review (CDR) review. For the current RfA report, database searches were rerun on April 29, 2019 to capture any articles published after the search date of the original RfA. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on June 19, 2019.

Grey literature (literature that is not commercially published) was identified through a limited search of relevant websites found in the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):[12] drug and devices regulatory approvals, advisories and warnings, clinical trials registries, and databases (free). Google was used to search for additional Internet-based materials.

Review Methods

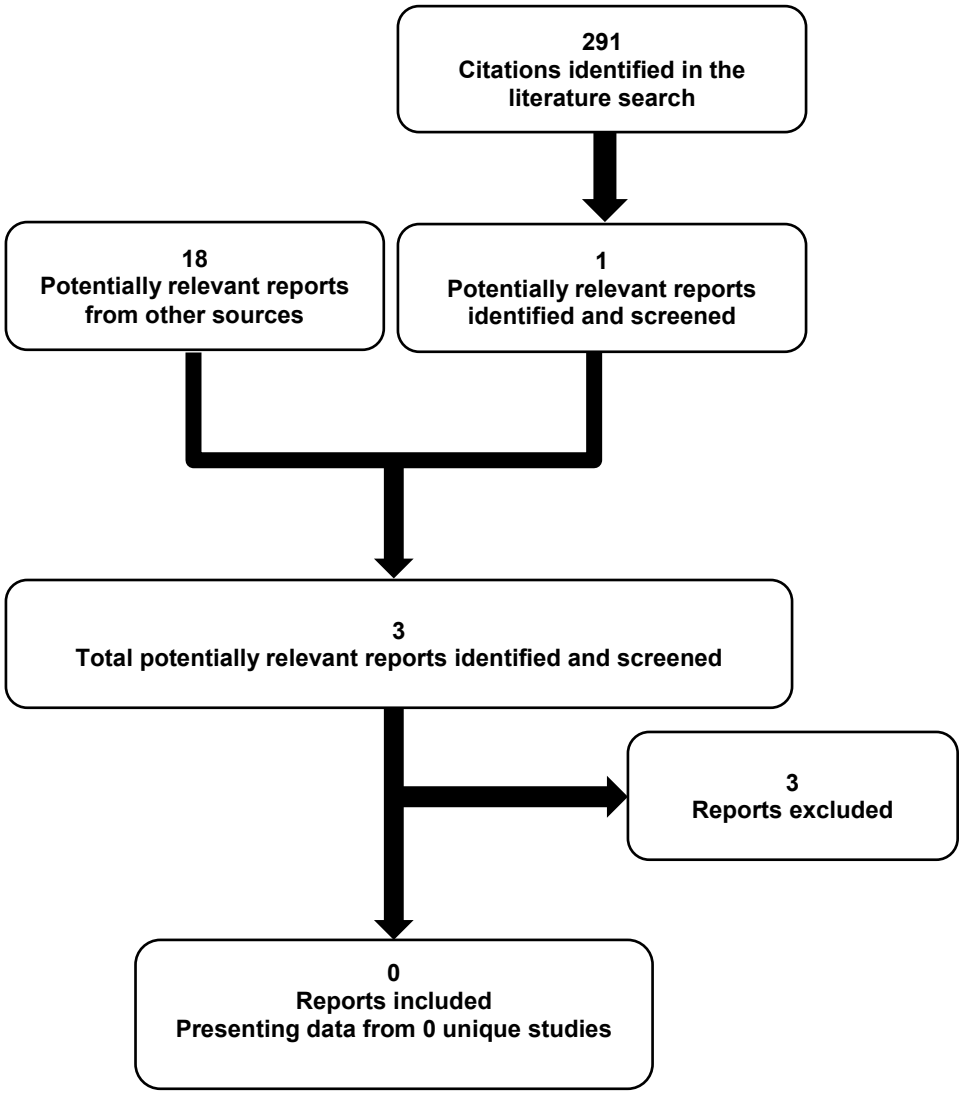
Phase III randomized controlled studies were selected for inclusion based on the selection criteria presented in Table 2. One CADTH CDR clinical reviewer independently selected studies for inclusion in the review based on titles and abstracts according to the predetermined protocol. Full-text articles of all citations considered potentially relevant were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through consensus. Included studies are presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient Population	Adult women of reproductive age with moderate-to-severe signs or symptoms from UFs	
Intervention	Repeated, 3-months courses of UA 5 mg daily	
Comparators	**Hormonal:** • GnRH agonists • Combined hormonal contraceptives • Progestin-releasing intrauterine system • Progestins	**Non-hormonal:** • Tranexamic acid • NSAIDs **Other:** • Placebo • Watchful waiting
	Surgical: • Hysterectomy • Myomectomy • Uterine artery occlusion • Myolysis	**Non-surgical:** • Uterine artery embolization • MRI-focused ultrasound
Outcomes	**Key efficacy outcomes:** • PBAC (menstrual blood loss) • Amenorrhea **Other efficacy outcomes**: • Number (%) of patients proceeding to surgery after or during treatment • Number (%) of invasive surgeries (i.e., laparoscopic hysterectomy) • Control of bleeding • Alkaline hematin test (menstrual blood loss) • Time to control bleeding • Quality of life by validated instrument • Symptom control (i.e., pain or discomfort) • Reversal of anemia, if present (Hgb/Hct, ferritin) • Total myoma volume • Uterine volume **Harms outcomes**: AEs, SAEs, WDAEs, mortality, notable harms (i.e., endometrial hyperplasia/carcinoma, VTE)	
Study Design	Published and unpublished RCTs	

AE = adverse events; GnRH = gonadotropin-releasing hormone; Hct = hematocrit; Hgb = hemoglobin; MRI = magnetic resonance imaging; NSAIDs = nonsteroidal anti-inflammatory drugs; PBAC = Pictorial Blood Loss Assessment Chart; RCT = randomized controlled trial; SAE = serious adverse events; UA = ulipristal acetate; UF = uterine fibroid; VTE = venous thromboembolism; WDAE = withdrawal due to adverse events.

Figure 1: QUOROM[a] Flow Diagram for Inclusion and Exclusion of Studies



[a] Quality of Reporting of Meta-analyses

Appendix 2: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) Embase (1974 to present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	April 29, 2019
Alerts:	Weekly search updates until project completion
Study Types:	No filters were applied to limit retrieval by study type
Limits:	Publication date limit: 2016 to present Humans Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(6J5J15Q2X8 or YF7V70N02B).rn,nm.
2	(ulipris* or esmya* or fibristal* or va 2914 or va2914 or CBD 2914 or CBD2914 or CDB 2914 or CDB2914 or HRP 2000 or HRP2000 or RTI 3021-012 or RTI 3021012 or RTI3021012 or RU 44675 or RU44675 or Logilia* or ellaone* or ella one* or PGL 4001 or PGL4001).ti,ab,kf,ot,hw,nm,rn.
3	or/1-2
4	3 use medall
5	*Ulipristal/
6	(ulipris* or esmya* or fibristal* or va 2914 or va2914 or CBD 2914 or CBD2914 or CDB 2914 or CDB2914 or HRP 2000 or HRP2000 or RTI 3021-012 or RTI 3021012 or RTI3021012 or RU 44675 or RU44675 or Logilia* or ellaone* or ella one* or PGL 4001 or PGL4001).ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	(Conference abstract or conference review).pt.
10	8 not 9
11	4 or 10
12	exp animals/
13	exp animal experimentation/ or exp animal experiment/
14	exp models animal/
15	nonhuman/
16	exp vertebrate/ or exp vertebrates/
17	or/12-16
18	exp humans/
19	exp human experimentation/ or exp human experiment/
20	or/18-19
21	17 not 20
22	11 not 21
23	remove duplicates from 22
24	limit 23 to yr="2016 -Current"

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials Search terms used: Fibristal, ulipristal, Ella, and Esmya	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms used: Fibristal, ulipristal, Ella, and Esmya	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used	

Grey Literature

Dates for Search:	April 30, 2019
Keywords:	Fibristal (and synonyms)
Limits:	Publication years: 2017 to present

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Clinical Trial Registries
- Databases (free)
- Internet Search

Appendix 3: CDEC Recommendation

Indication: Uterine fibroids

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated November 15, 2013.

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ulipristal acetate be reimbursed for the treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery, and for the intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age, with the duration of each treatment course being three months, if the following conditions are met:

Conditions

- The patient is under the care of an obstetrician/gynecologist.
- Treatment should be limited to a maximum of four courses of therapy.

Reasons for the Recommendation

- In two trials reviewed in the original submission of ulipristal acetate for the treatment of uterine fibroids (PEARL I and PEARL II), one three-month treatment course of ulipristal acetate was shown to be superior to placebo and noninferior to leuprolide acetate for decreasing menstrual bleeding in patients with uterine fibroids.
- Results from one double-blind, multi-centre, randomized, dose-controlled trial (PEARL IV; N = 451) in premenopausal women with uterine fibroids indicated that, after four courses of treatment with ulipristal acetate, 49% of patients achieved amenorrhea. Patients also experienced a reduction in the Pictorial Blood Loss Assessment Chart (PBAC) score and a reduction in median fibroid size from baseline. No major safety concerns were reported in PEARL IV, and the safety profile was similar to what was reported in the PEARL I and PEARL II trials.
- The efficacy and safety of ulipristal acetate beyond four courses of treatment is uncertain.

Of Note

- CDEC noted that the drug plan costs for ulipristal acetate when used as a treatment based on the original indication (i.e., as a treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery, for a duration of three months, with treatment limited to one course of therapy) should still not exceed the drug plan costs for the manufacturer's identified comparator, leuprolide acetate, as specified in the original CDEC recommendation.
- CDEC noted that, based on the updated indication for ulipristal acetate, the CADTH Common Drug Review (CDR) reanalysis found six months of treatment with leuprolide acetate, followed by abdominal hysterectomy, to be more effective but costlier than four courses of ulipristal acetate with an incremental cost per quality-adjusted life-year (QALY) gain of $25,158. This value of the incremental cost per QALY gained is within a range that is normally considered by CDEC to reflect cost-effective treatment options, which suggests that treatment with leuprolide acetate prior to hysterectomy is the optimal therapeutic choice. However, the manufacturer did not include any utility benefit from avoiding hysterectomy for women who wish to preserve their uterus. As this is an option that many patients would prefer compared with undergoing surgery (based on input from patient groups and input from the clinical expert consulted for this review), the inclusion of such a utility benefit would have decreased the cost-effectiveness of treatment with six months of leuprolide acetate prior to hysterectomy. When combined with uncertainty around the cost-effectiveness estimate for the treatment with leuprolide acetate, failure to consider any potential utility benefits because of the avoidance of surgery increases the likelihood that the incremental cost per QALY gained of treatment with six months of leuprolide acetate prior to hysterectomy will exceed $25,000. Therefore, it is unclear whether six months of treatment with

leuprolide acetate prior to hysterectomy is a more cost-effective option compared with four courses of ulipristal acetate. The committee also recognized that four courses of ulipristal acetate should have been compared with a wider range of treatment options (e.g., abdominal hysterectomy or embolization) in the cost-effectiveness analysis. However, additional economic analyses were limited because of the lack of comparative clinical information and, as such, the economic impact of the use of ulipristal acetate on the health care system remains uncertain.

Discussion Points

- CDEC noted that abnormal uterine bleeding is a common concern for patients with uterine fibroids — a symptom for which non-invasive options other than ulipristal acetate are available (e.g., oral contraceptives, intrauterine devices). CDEC also noted that other less invasive surgical treatments (e.g., myomectomy) remain an option for women with uterine fibroids for the treatment of associated moderate-to-severe signs and symptoms, as per the Society of Obstetricians and Gynaecologists of Canada 2015 guidelines on the management of uterine fibroids.
- CDEC received patient input suggesting there is a need for non-invasive therapy that results in avoidance of surgery (e.g., hysterectomy) and that this would be beneficial for those wanting to preserve fertility. However, there is no evidence to assess the impact of ulipristal acetate on fertility in these patients.
- CDEC noted that selecting a more specific population(s) of patients that would achieve the most benefit from this drug may improve the overall cost-effectiveness for public drug plans. However, the limited clinical data available to inform these analyses precluded the committee from identifying specific population(s) of patients for whom ulipristal acetate may be the most cost-effective treatment option.
- CDEC noted that there is no evidence to support the use of 5 mg of ulipristal acetate as a re-treatment option subsequent to being used for four courses of treatment.
- CDEC recognized that one small (N = 64), single-arm, open-label study (PEARL III) in which patients were administered 10 mg of ulipristal acetate for up to eight consecutive courses of treatment did not identify any safety concerns; however, the 10 mg dose of ulipristal acetate is not approved by Health Canada.
- CDEC noted that only 5.3% of participants in the PEARL IV study were black, whereas uterine fibroids in black women, compared with white women, are two to three times more common, are larger at diagnosis, and are associated with more severe symptoms. Thus, the efficacy of ulipristal acetate in a population of women who are likely to have the greatest need for treatment remains uncertain.

Background

Ulipristal acetate has a Health Canada–approved indication for the treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery, and an intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age. The duration of each treatment course is three months, with an approved dose of 5 mg per day. Ulipristal acetate is an orally active selective progesterone receptor modulator.

The CDR-participating drug plans submitted a RfA to CADTH with respect to the 2013 CDEC recommendation for ulipristal acetate for the treatment of uterine fibroids, requesting that CDEC provide advice regarding the following:

- Should the CDEC recommendation for ulipristal acetate (Fibristal) be updated to address the revised indication (i.e., intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age)?
- Should the CDEC recommendation for ulipristal acetate (Fibristal) be updated to address the revised dosage regimen (i.e., the duration of each treatment course is three months)?

Submission History

In 2013, CDEC recommended that ulipristal acetate be listed according to the Health Canada indication at the time of the recommendation (i.e., for the treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery), if the following conditions are met:

- The duration of treatment with ulipristal acetate should not exceed three months.
- The patient is under the care of an obstetrician/gynecologist.
- The drug plan costs for ulipristal acetate should not exceed the drug plan costs for the manufacturer's identified comparator, leuprolide acetate.

View the full 2013 CDEC recommendation here: https://cadth.ca/sites/default/files/cdr/complete/complete_SR0326_Fibristal_19-Nov-13_e.pdf.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of ulipristal acetate, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

Two patient groups responded to the CDR call for patient input — the Women's Health Initiative Network and Canadian Women with Fibroids (CANFib). The following is a summary of information provided by the patient groups:

- Aside from Fibristal, there is no long-term medical therapy available that decreases the fibroid size, has tolerable side effects, and maintains fertility. This is especially important for women who are not eligible for surgery because of anemia, obesity, or other comorbidities that would make surgery unadvisable, or for women who wish to avoid surgery.
- The treatment of uterine fibroids can be medical or surgical in nature, each with varying degrees of effectiveness and adverse events. Non-surgical approaches are either short-term and meant to shrink the fibroid before surgery or are used to control symptoms of bleeding or pain. Of the 416 patients surveyed by CANFib, 63% wanted to avoid surgery completely and 76% wanted to retain their uterus.
- Patients expressed a strong preference for conservative treatment options that provide bleeding control, are easy to administer, avoid surgery whenever possible, and reduce pain and bulking (i.e., bloating, abdominal pressure). Some patients also expressed a desire for therapies that bridge to menopause without surgery, avoiding the associated complications altogether.

Clinical Trials

The systematic review included one double-blind, randomized, dose-controlled trial (PEARL IV study, N = 451) of patients with uterine fibroids. Enrolled patients were randomized in a 1:1 ratio to either four treatment courses of 5 mg of ulipristal acetate once daily or 10 mg of ulipristal acetate once daily. Each treatment course lasted for three months, between which patients were off-treatment and the subsequent treatment course would start when the second menses began. PEARL IV included European patients who were premenopausal and had an average-sized uterine fibroid (a 3 cm diameter and 12-cm diameter, diagnosed by ultrasound), with excessive menstrual bleeding (PBAC score greater than 100), and with no major comorbidities and no history of prior hormonal treatment or immediate history of radiological or surgical interventions. Of the two ulipristal acetate treatment groups, it is the 5 mg group that reflects the Health Canada–approved recommended dose for ulipristal acetate and, as such, only descriptive results for the 5 mg treatment group are presented here.

The main limitation of the PEARL IV trial that may affect the internal validity of the results is the high attrition rate in the trial. More than 20% of the patients dropped out, mostly because of "subject request." Other patients who withdrew did so for a variety of

reasons including lack of efficacy, pregnancy, and adverse events. Other limitations include the lack of a control group to the 5 mg ulipristal group, and the lack of data on the long-term safety and efficacy of ulipristal acetate beyond four courses of treatment.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- the percentage of patients who achieve amenorrhea at the end of each of the treatment courses and at the end of all of the treatment courses
- change in the PBAC score
- changes in quality of life and symptoms as measured through the Uterine Fibroid Symptom & Health-Related Quality of Life (UFS-QoL) Questionnaire, and assessment of pain on a visual analogue scale
- changes in fibroid and uterine volumes
- serious adverse events, total adverse events, and withdrawals due to adverse events.

The co-primary outcomes in the PEARL IV study were the proportion of patients achieving amenorrhea at the end of the first two treatment cycles (part I), and the proportion of patients achieving amenorrhea at the end of four treatment cycles (part II).

Results

Efficacy

At the end of the four treatment courses, 48.7% of the patients (95 out of 195) in the 5 mg group were identified as achieving amenorrhea. Sensitivity analyses conducted with this population showed that, when missing data were imputed as failures, the proportion of patients that achieved amenorrhea was 41.7% (95 out of 228); when missing data were assumed to be successes, the proportion of patients that achieved amenorrhea was 49.1% (112 out of 228). The PBAC score showed a decrease from a mean of 300.2 at baseline to 139.7 after four courses of treatment, 76.6% of patients (121 out of 158) achieved a 25% or more reduction in the fibroid size at the end of the follow-up, and patients experienced numerical improvements in their median UFS-QoL symptoms severity score during treatment. Patients tended to demonstrate fewer numerical improvements in the off-treatment period compared with the period immediately following the conclusion of a treatment course; however, the clinical significance of these findings is unclear because of the lack of a minimal clinically important difference. No established minimal clinically important difference was available for the proportion of patients with amenorrhea, change in the PBAC score, change in UFS-QoL, change in pain score, or change in fibroid or uterine size.

Harms (Safety and Tolerability)

Most treatment-emergent adverse events were reported during the first course of treatment, with 102 patients out of 230 (44.3%) reporting at least one adverse event in the 5 mg group. Subsequently, this percentage is recorded at 27.4%, 16.6%, and 23.9% for the second, third, and fourth course of treatment, respectively. Headaches were the most commonly reported adverse event, followed closely by hot flushes, which also decreased in incidence with subsequent treatment courses. Overall, 16 patients (7%) discontinued their treatment from the 5 mg group during the study because of adverse events. Serious adverse events were reported as five cases of menorrhagia, one case of bipolar disorder, one case of spontaneous myoma expulsion, one case of abdominal pain, and one case of back pain.

No drug-related deaths were reported in the study. Endometrial hyperplasia was reported in three patients in the 5 mg group. An undefined endometrial malignant neoplasm was reported once in the 5 mg group. It was later diagnosed as a case of endometrial adenocarcinoma, which was believed to have been pre-existing.

Cost and Cost-Effectiveness

Ulipristal acetate is available as a 5 mg tablet at the list price of C$11.46. At the recommended dose of 5 mg daily for three months, the cost of a 90-day course of treatment is C$1,031. While not specifically indicated for the treatment of signs and symptoms of

uterine fibroids, leuprolide acetate may be used once monthly (as a 3.75 mg injection) or once every three months (as a 11.25 mg injection) for up to six months to manage this condition, at a cost of C$1,071 to C$1,078.

In response to a request from CADTH, the manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing four courses of ulipristal acetate (four courses of three months on treatment and two months off-treatment), with one course of ulipristal acetate (three months on treatment, then two months off) followed by leuprolide acetate, over a 20-month time horizon. The manufacturer also considered an additional analysis comparing ulipristal acetate (four courses) with abdominal hysterectomy (where leuprolide acetate was used six months for pre-surgical treatment). In the manufacturer's base-case analysis, the regimen of four courses of ulipristal acetate was dominant over a single course of treatment with ulipristal acetate followed by monthly injections of leuprolide acetate; namely, ulipristal acetate costs less (C$4,606 versus C$7,486) and is more effective (1.113 quality-adjusted life-years [QALYS] versus 1.109 QALYs). In the scenario analysis, an abdominal hysterectomy cost more but was associated with greater QALYs than ulipristal acetate, resulting in an incremental cost-utility ratio of C$3.9 million per QALY for abdominal hysterectomy and suggesting that abdominal hysterectomy is not cost-effective compared with ulipristal acetate.

A number of limitations were noted by CADTH in the economic evaluation. This included the choice of time horizon (20 months), which captured the four courses of ulipristal acetate treatment but excluded how patients were to be managed after the 20-month period, such as addressing the possibility of requiring abdominal hysterectomy. The base-case analysis also did not include the possibility of an abdominal hysterectomy during the 20-month time horizon for either treatment group. In addition, the manufacturer's base-case analysis specifically reflects a patient population seeking to preserve their uterus (i.e., delay hysterectomy). This may not be reflective of the full indicated population. Given that the new Health Canada indication is not only for women requiring a hysterectomy to manage their symptoms, this cost-effective analysis is incomplete, as it did not compare ulipristal acetate to other acceptable treatment options. For the full eligible population, four courses of ulipristal acetate should have been compared with a wider range of treatment options, including abdominal hysterectomy and embolization in the base case. Further, to capture the benefits of preserving the uterus, utility benefits associated with the preservation should have been included, as this value may differ, depending on whether the preservation of the uterus was for the purposes of maintaining fertility or some other rationale.

CADTH was able to address some of the limitations identified with the manufacturer's economic submission:

- It was assumed that a proportion of women receiving ulipristal acetate would require an abdominal hysterectomy after four courses were complete (based on the rate of uncontrolled bleeding from the PEARL IV study).
- A 40-month time horizon was adopted to incorporate the costs and benefits from subsequent surgery.
- The analysis compared four courses of ulipristal acetate followed by a proportion requiring hysterectomy (when deemed necessary) with six courses of leuprolide acetate followed by abdominal hysterectomy as a more appropriate comparison.

Based on the reanalysis, CADTH suggests that intermittent treatment with ulipristal acetate (four courses) was both less effective and less costly than six months' treatment with leuprolide acetate followed by abdominal hysterectomy. The incremental cost per QALY gained for six months' treatment with leuprolide acetate followed by abdominal hysterectomy, compared with intermittent treatment with ulipristal acetate (four courses), was C$25,158 per QALY. Thus, if a decision-maker is willing to pay at least C$25,158 per QALY gained, treatment with leuprolide acetate prior to hysterectomy is preferred compared with intermittent treatment with ulipristal acetate.

The preceding reanalysis does not include any utility benefit from avoiding hysterectomy for women who wish to preserve their uterus. However, no such data were provided by the manufacturer. Similarly, the design of the manufacturer's economic model did not permit an analysis comparing four courses of ulipristal acetate followed by a proportion requiring hysterectomy (when deemed necessary) with one course of ulipristal acetate followed by a proportion requiring hysterectomy when deemed necessary. The inflexibility of the submitted model, the lack of comparative data, and the lack of long-term data on the need for hysterectomy results in a CADTH reanalysis that remains speculative.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 18, 2017 Meeting

Regrets

None

Conflicts of Interest

None

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