CADTH

CADTH COMMON DRUG REVIEW

Request for Advice

Ulipristal Acetate (Fibristal)

(Allergan Inc.)

Indication:

- 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.

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CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
FAS	full analysis set
HRQoL	health-related quality of life
IQR	interquartile range
PBAC	pictorial blood-loss assessment chart
PP	per-protocol
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RfA	request for advice

Drug	Ulipristal acetate (Fibristal)
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.
Request for Advice Questions	1. Should the CDEC recommendation for ulipristal acetate (Fibristal) be updated to address the addition of a new population in the revised indication (i.e., intermittent treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age)? 2. 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 3 months)?
Manufacturer	Allergan Inc.

Executive Summary

Introduction

The CADTH Common Drug Review (CDR)–participating drug plans have submitted a request for advice (RfA) to CADTH regarding the 2013 recommendation for ulipristal acetate (Fibristal) for the treatment of uterine fibroids. In November 2013, CADTH issued a CADTH Canadian Drug Expert Committee (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.
- 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.

Since this recommendation was issued, both the indication and treatment regimen for ulipristal acetate have been revised, no longer restricting the patient population to those eligible for surgery and allowing for intermittent three-month treatment courses instead of one three-month treatment course.

Initial 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. The duration of treatment is limited to 3 months.
Revised 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.

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

1. 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)?

2. 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)?

Results and Interpretation

Included Studies

PEARL IV was a randomized controlled trial where patients with uterine fibroids were randomized into four treatment courses of 5 mg or 10 mg ulipristal acetate once daily. Each treatment course lasted for three months, between which patients were off treatment. 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 (between 3 cm and 12 cm in diameter, diagnosed by ultrasound), with excessive menstrual bleeding (pictorial blood-loss assessment chart [PBAC]) score > 100), and with no major comorbidities and no history of prior hormonal treatment or immediate history of radiological or surgical interventions. Descriptive statistics were provided for all outcomes using proportions in categorical outcome and means in continuous outcomes. The authors conducted comparative statistical analysis with the 10 mg control arm. However, the 10 mg arm cannot be considered an appropriate control comparison as it cannot provide any information regarding the efficacy of the approved 5 mg dose as compared with no treatment, placebo, or a practised active control. We only present here the results of the 5 mg arm.

A main limitation 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 due to “subject request.” Other patients who withdrew did so for a variety of reasons, including lack of efficacy, pregnancy, and adverse events (AEs). However, several sensitivity analyses were carried out to assess the impact of the missing data on the primary outcome. Other limitations include the lack of a control arm to the 5 mg ulipristal acetate arm and the lack of data on the long-term safety and efficacy of ulipristal acetate beyond four courses of treatment.

Efficacy

At the end of the four treatment courses, 48.7% of the patients (95 out of 195) in the 5 mg arm were identified as being in amenorrhea. Sensitivity analyses conducted with this population showed that when missing data were imputed as failures, then the proportion of patients that achieved amenorrhea was 41.7% (95 out of 228); when missing data were assumed to be successes, then the proportion of patients that achieved amenorrhea was 49.1% (112 out of 228). PBAC showed a drop from a mean of 300.2 at baseline to 139.7 after treatment course 4, 76.6% of patients (121 out of 158) achieved a 25% or more reduction in fibroid size at the end of the follow-up, and patients experienced improvements in their Uterine Fibroid Symptom and Health-Related Quality of Life symptoms severity score during treatment.

The lack of an appropriate comparative group negates our ability to draw statistical inferences with any certainty into the general population. In the absence of direct evidence, the manufacturer submitted an indirect treatment comparison based [redacted]

Harms

Most treatment-emergent AEs were reported during the first course of treatment, with 102 patients out of 230 (44.3%) reporting at least one AE in the 5 mg arm. Subsequently, this percentage is recorded at 27.4%, 16.6%, and 23.9% for treatment courses 2, 3, and 4, respectively. Headaches were the most commonly reported AE, followed closely by hot flushes, although both AEs followed the general trend of decreasing with subsequent treatment courses. Overall, 16 patients (7%) discontinued their treatment from the 5 mg arm during the study due to AEs. 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 arm. An undefined endometrial malignant neoplasm was reported once in the 5 mg arm. It was later diagnosed as a case of endometrial adenocarcinoma and was believed to have been pre-existing.

Other Considerations

The input received from patient groups identified patients who might not have been eligible for surgery. These would usually include anemic patients, patients suffering from obesity, and patients with bleeding abnormalities. As identified in the patient input, these patients experienced significant relief from long-term intermittent therapy with ulipristal acetate. In addition, as outlined in Subsection 4.2, Place in Therapy, there is an unmet need to be addressed in patients who wish to maintain fertility, are ineligible for surgery, wish to avoid

surgery, or wish to reduce symptoms until reaching menopause. No available alternative medical therapy exists that can be administered in the long term and for which evidence suggests reduced fibroid size.

Economic Information

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 (Lupron), over a 20-month time horizon. 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 — four courses cost less ($4,606 versus $7,486) and are more effective (1.113 quality-adjusted life-years [QALYs] versus 1.109 QALYs).

CADTH noted a number of limitations with the economic evaluation. This included the choice of time horizon (20 months), which captured the four courses of ulipristal acetate treatment, but excluded consideration of how patients will be managed after the 20-month period, addressing issues such as the possibility of requiring abdominal hysterectomy. The base-case analysis did not include the possibility of an abdominal hysterectomy during the 20-month time horizon for either treatment arm. Also, 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. For the full population, four courses of ulipristal acetate should have been compared with a wider range of treatment options, including abdominal hysterectomy and embolization.

CADTH was able to address some of the limitations identified with the manufacturer's economic submission, but the inflexibility of the submitted model, the lack of comparative data, and the lack of long-term data on the need for a hysterectomy resulted in a CADTH reanalysis that remains speculative. 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 followed by abdominal hysterectomy compared with intermittent treatment with ulipristal acetate (four courses) was $25,158 per QALY. Thus, if a decision-maker is willing to pay at least $25,158 per QALY gained, treatment with leuprolide acetate prior to hysterectomy is preferred over 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).

Conclusions

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.
- 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.

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. CADTH received an RfA from the CDR-participating drug plans, asking 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-centre, randomized, dose-controlled trial (PEARL IV, N = 451) in premenopausal women with uterine fibroids between 3 cm and 12 cm in diameter, inclusive, with heavy menstrual bleeding > 100 PBAC and uterine size < 16 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 three months, between which patients were off treatment.[2,3] The CDR review focused on the results of the 5 mg treatment arm, as this aligns with the Health Canada–approved indication. The efficacy results from PEARL IV indicated that 48.7% of patients (95 out of 195) achieved amenorrhea after four treatments; as well, patients experienced a reduction in PBAC score from a mean of 300.2 at baseline down to a mean of 139.7 and a 67% reduction in median fibroid size from baseline.[2,3] No major safety signals were reported in PEARL IV; the safety profile was similar to what has been reported in PEARL I and II and, according to the clinical expert consulted for this review, 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 treatment comparison that was based [redacted].

Based on 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' 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 $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 a hysterectomy resulted in a CADTH reanalysis that remains speculative.

Table 1: Summary of Results

	Ulipristal Acetate 5 mg (FAS1 Unless Stated Otherwise, N = 228)
Proportion of Patients Who Achieved Amenorrhea	
Amenorrhea at the end of all four treatment courses, n/N (%)	95/195 (48.7%)
Amenorrhea at the end of all four treatment courses, n/N (%) (FAS 4)	94/150 (62.7%)
PBAC Scores	
First menses post-screening, baseline actual, mean (median)	300.2 (224.0)
First menses post–treatment course 4, mean (median)	139.7 (77.5)
Fibroid Volume Reduction ≥ 25%	
Post–first menses after treatment course 4, n/N (%)	125/160 (78.1%)
Change from Baseline in UFS-QoL Score	
Start of treatment course 1 (baseline), median (IQR)	50.0 (37.5 to 62.5)
End of treatment course 4, CFB median (IQR)	−31.3 (−46.9 to −12.5)
After treatment course 4, CFB median (IQR)	−21.9 (−40.6 to −9.4)
Follow-up, CFB median (IQR)	−28.1 (−40.6 to −9.4)
Assessment of Pain on a Visual Analogue Scale	
Start of treatment course 1 (baseline), median (IQR)	39.0 (15.6 to 62.0)
End of treatment course 4, CFB median (IQR)	−20.0 (−46.1 to −0.5)
After treatment course 4, CFB median (IQR)	−16.0 (−38.0 to 1.0)
Follow-up, CFB median (IQR)	−16.0 (−44.0 to 4.0)

FAS = full analysis set; IQR = interquartile range; N = total number in the sample under study; n = number in a subgroup of the sample under study; PBAC = pictorial blood-loss assessment chart; CFB = change from baseline; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.

Background

The Recommendation, Reason(s) for the Recommendation, and Of Note sections in the 2013 CADTH Canadian Drug Expert Committee (CDEC) recommendation for Fibristal for uterine fibroids state the following:[1]

Recommendation

CDEC recommends that ulipristal acetate 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:

Conditions:

- 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.

Reason(s) for Recommendation

1. In two double-blind randomized controlled trials (RCTs) ulipristal acetate was shown to be superior to placebo (PEARL I) and noninferior to leuprolide acetate (PEARL II) for decreasing menstrual bleeding in patients with uterine fibroids. In addition, ulipristal acetate was associated with fewer adverse events than leuprolide acetate in PEARL II.
2. At the submitted price, ulipristal acetate ($1,031 per three-month course) is less costly than leuprolide acetate ($1,042 per three-month course).

Of Note

There were no data available in the included RCTs for patients with uterine fibroids who had previously been treated with gonadotropin-releasing hormone (GnRH) analogues.

The primary conclusions for the 2013 CADTH Common Drug Review (CDR) clinical review were as follows:[4]

"In two phase III RCTs [randomized controlled trials], ulipristal was shown to reduce uterine bleeding in a greater percentage of patients than placebo in PEARL I and to a similar extent as GnRH [gonadotropin-releasing hormone] agonist (i.e., leuprolide) therapy in PEARL II; hence, ulipristal was found to be noninferior to leuprolide, based on the pre-specified noninferiority margin of –20% in PEARL II. There were no clear differences between groups in quality of life or non-menstrual bleeding symptom control outcomes detected during 13 weeks of treatment in either study. A large proportion of surgeries were not completed as planned following preoperative study drug treatment, the reasons for which were not provided. Ulipristal treatment appeared generally well tolerated, with comparatively low incidence of WDAEs [withdrawals due to adverse events] and SAEs [serious adverse events]. Of the two trials, headache and hot flashes were the most frequently presenting AEs for ulipristal-treated patients, but neither these nor any other AEs occurred more frequently than observed in the comparator group. However, long-term safety data (beyond three months) for ulipristal is lacking.

"Key limitations of the evidence included the lack of North American patients studied, which may reduce generalizability; the lack of pre-specified surgical end points, which limits the ability to fully evaluate ulipristal's potential place in therapy; and a lack of data demonstrating superiority over placebo on validated quality of life instruments — quality of life was identified as a patient-important outcome for this review."

The full recommendation can be found in Appendix 2.

Request for Advice

The CDR-participating drug plans have submitted a request for advice (RfA) to CADTH regarding the 2013 recommendation for ulipristal acetate (Fibristal) for the treatment of uterine fibroids. 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:

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

1. 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)?
2. 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)?

CDR Approach to the Request for Advice

In order to address the RfA questions, the CDR review team updated the systematic review in the 2013 clinical report for the uterine fibroids indication to include clinical data that are relevant to the updated indication of ulipristal acetate.

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.

Clinical Findings

Assessment of Evidence

A total of 473 studies was identified from the literature for inclusion in the systematic review and one study (PEARL IV) met the selection criteria for the review. Pearl IV is summarized in Table 2 and described in the following sections. A list of excluded studies is presented in Appendix 4.

Table 2: Details of Included Studies

		PEARL IV
Design & Population	**Study Design**	Double-blind, randomized, dose-controlled, parallel group, multi-centre clinical trial
	Locations	Europe
	Randomized (N)	451
	Inclusion Criteria	• Premenopausal woman between 18 and 50 years of age • BMI between 18 and 40 • FSH levels ≤ 20 mIU/mL • Excessive uterine bleeding attributed to uterine fibroids • Regular menstrual cycles • Uterus size less than 16 weeks with at least 1 fibroid ≥ 3 cm in diameter • The use of a non-hormonal method of contraception in cases of child-bearing potential
	Exclusion Criteria	• History of uterus surgery that would interfere with the study end points • Less than 6 months' history of uterine artery embolization • History of or current uterine, cervical, ovarian, or breast cancer • History of or current adenocarcinoma or endometrium atypical hyperplasia • Existing uterine polyps > 2 cm • Existing severe coagulation disorder • Existing ovarian cysts ≥ 4 cm • History of uterine fibroid treatment with selective progesterone receptor modulator • Existing abnormal hepatic function at study entry • Has tested positive for pregnancy, is nursing, or is planning a pregnancy during the course of the study • Is currently taking 1 of the following prohibited medications: progestins, ASA, mefenamic acid, anticoagulants, or gonadotropin-releasing hormone agonists or antagonists
Drugs	**Intervention**	• 5 mg ulipristal acetate, daily, orally
	Comparator(s)	• 10 mg ulipristal acetate, daily, orally

		PEARL IV
Duration	**Phase**	
	Run-in	NR
	Double-blind	20 months
	Follow-up	3 months
Outcomes	**Primary End Points**	• Amenorrhea at the end of the first 2 treatment courses (part I) • Amenorrhea at the end of all 4 treatment courses (part II)
	Other End Points	• Amenorrhea at the end of each individual treatment course (1, 2, 3, and 4) • Change in bleeding patterns by PBAC • Volume of 3 largest fibroids • Assessment of pain using a visual analogue scale • Assessment of quality of life using UFS-QoL
Notes	**Publications**	Donnez et al. 2014,[5] Donnez et al. 2016,[2] Fibristal (ulipristal acetate): tablet, 5 mg [product monograph][6]

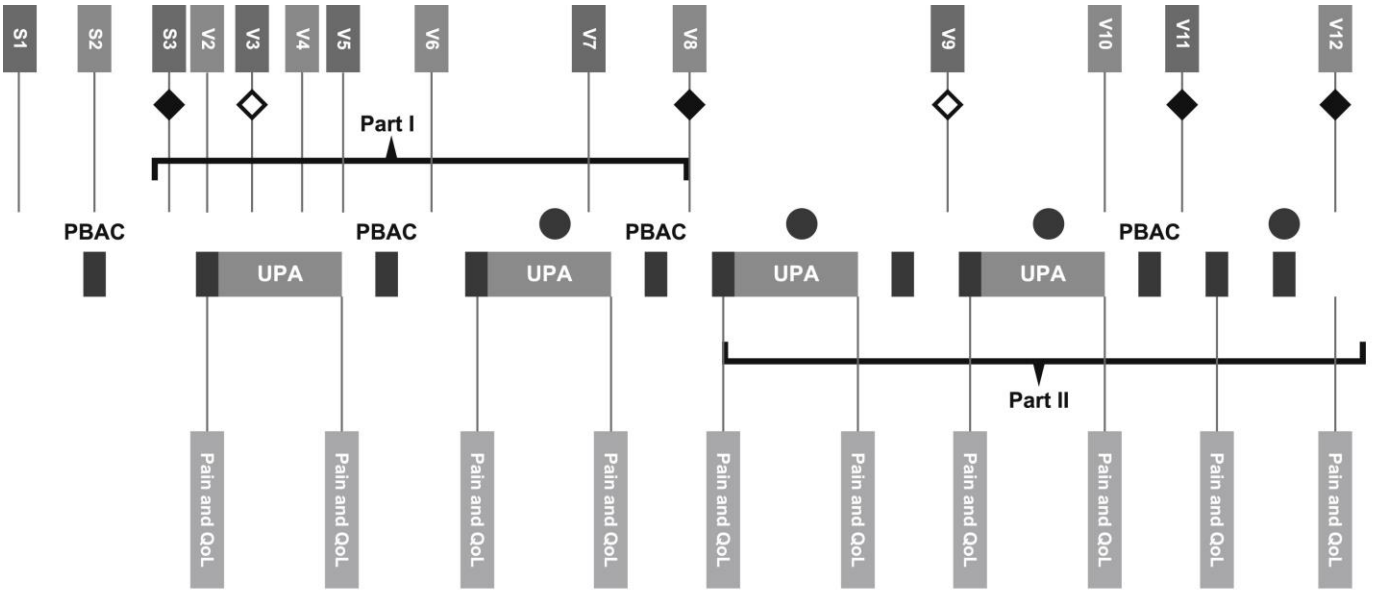
BMI = body mass index; FSH = follicle-stimulating hormone; N = total number in the sample under study; NR = not reported; PBAC = pictorial blood-loss assessment chart; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.
Source: Donnez et al. 2014,[5] Donnez et al. 2016,[2] Fibristal (ulipristal acetate): tablet, 5 mg [product monograph].[6]

Included Studies

Description of Studies

PEARL IV was an RCT where patients with uterine fibroids were randomized into four treatment courses of 5 mg or 10 mg ulipristal acetate once daily. Each treatment course lasted three months, between which patients were off treatment. The subsequent treatment course would start when the second menses began. Figure 1 provides a visual representation of the study design and outcomes. The trial was planned in two parts: The objective of the first part was to assess the efficacy of ulipristal acetate after two courses, while the second part assessed the results of four treatment courses. The results of the four treatment courses are presented here.

Figure 1: Flow Diagram of the Study Design of PEARL IV



S1 1st visit to site, can be anytime. Subject trained to use ediary
S2 During menses
S3 10-18 days after menses

V2 1-4 days after start menses
V3 28 days after V2
V4 28 days after V3
V5 28 days after V4 (end of treatment 1)
V6 10-18 days after menses following treatment 1

V7 End of treatment 2 (equivalent V5)
V8 10-18 days after menses following treatment 2
V9 10-18 days after menses following treatment 3
V10 End of treatment 4
V11 10-18 days after menses following treatment 4
V12 Follow-up 3 months after last dose (mid-cycle)

Diary:
Bleeding: PBAC or simplified
Medication intake
Prompts for visits and meds
UFS QoL, pain VAS

UPA — UPA 5mg/10mg
Menses
PBAC — Record PBAC
Endometrium biopsy
Endometrium biopsy, (if previous not adequate)
Site call to patient

PBAC = pictorial blood-loss assessment chart; QoL = quality of life; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life; UPA = ulipristal acetate; VAS = visual analogue scale.
Source: Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub .Used under Creative Commons license CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International) CADTH does not own this work and permission should be sought from the copyright owner.[2]

Population

Inclusion and Exclusion Criteria

PEARL IV included European patients who were premenopausal and had an average-sized uterine fibroid (between 3 cm and 12 cm in diameter, diagnosed by ultrasound), with excessive menstrual bleeding (pictorial blood-loss assessment chart [PBAC]) score > 100), and with no major comorbidities and no history of prior hormonal treatment or immediate history of radiological or surgical interventions. Unlike PEARL I, PEARL II, and PEARL III,

there were no specific criteria in PEARL IV that restricted enrolment to patients who were eligible for surgery.

Baseline Characteristics

Table 3 provides a summary of major baseline characteristics. The mean age of all patients in the 5 mg ulipristal acetate full analysis set (FAS) 1 (N = 228) was 41.6 years (standard deviation 5.4), and the majority were white (92.5%). All treated patients in the 5 mg ulipristal acetate arm had a diagnosis of uterine leiomyoma. Prohibited medications included progestins, ASA, mefenamic acid, anticoagulants, antifibrinolytics, systemic glucocorticosteroids, and gonadotropin-releasing hormone agonists or antagonists. Concomitant medications were taken by a total of 131 patients (57.0%) in the 5 mg arm. The most frequently taken medications were anti-inflammatory/antirheumatic products, taken by 50 patients (21.7%); analgesics and antipyretics, taken by 44 patients (19.1%); and iron products, taken by 25 patients (10.9%).

Table 3: Summary of Baseline Characteristics (Full Analysis Set)

Characteristic	Ulipristal Acetate 5 mg (N = 228)
Age (years), mean (SD)	41.6 (5.4)
Ethnicity, n (%)	
Caucasian	211 (92.5)
Black	12 (5.3)
Other	4 (1.8)
Not reported	1 (0.4)
Weight (kg), mean (SD)	69.2 (12.7)
BMI (kg/m^2), mean (SD)	25.2 (4.1)
PBAC, median (IQR)	224 (148 to 357)
Total volume of 3 largest fibroids (cm^3), median (IQR)	42.6 (24.0 to 94.2)
Uterine volume (cm^3), median (IQR)	176.9 (113.1 to 269.8)
Pain assessment (VAS), median (IQR)	39.0 (15.6 to 62.0)
UFS-QoL questionnaire	
Symptom severity, median (IQR)	50.0 (37.5 to 62.5)
HRQoL, median (IQR)	56.9 (42.2 to 75.9)

BMI = body mass index; HRQoL = health-related quality of life; IQR = interquartile range; N = total number in the sample under study; PBAC = pictorial blood-loss assessment chart; SD = standard deviation; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life; VAS = visual analogue scale.
Source: Table adapted from Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub. Used under Creative Commons licence CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[2]

Interventions

Patients were randomized in a 1:1 ratio to either 5 mg or 10 mg of ulipristal acetate using a Web-integrated voice response system. Patients received the allocated medication in addition to matching placebo (part of allocation concealment) for four 12-week courses. Treatment began during the first four days of menses, and each course was separated by a drug-free interval. The drug-free interval lasted until the beginning of the second menses, when the next treatment course would start.

Outcomes

The primary outcome measured in the PEARL IV study was the percentage of patients in each arm who achieved amenorrhea after the first two treatment courses (part I) and at the end of all four treatment courses (part II). Amenorrhea was defined as no more than one day of spotting in a period of 35 days. Final assessment took place three months after the completion of the fourth course. Secondary end points of interest included the percentage of patients with amenorrhea after each treatment course, assessment of menstrual bleeding using the PBAC score, assessment of uterine fibroid size, assessment of pain, and assessment of health-related quality of life (HRQoL) using the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) tool.

The PBAC score is a series of diagrams representing bleeding patterns from lightly to heavily soiled tampons, towels, or pads with a grid to indicate the time of sanitation protection change. The previous Fibristal CDR review reported studies that demonstrated PBAC sensitivity ranging from 83% to 99% and specificity ranging from 7.5% to 89%.[4] No established minimal clinically important difference was reported.[4]

The USF-QoL has eight items on its symptom severity scale and 29 HRQoL items covering six domains: concern, activity, energy/mood, control, self-consciousness, and sexual function. Symptom severity and HRQoL items are scored on a 5-point Likert scale, with scores ranging from “not at all” to “a very great deal” for symptom severity and “none of the time” to “all of the time” for HRQoL. Scores are summed and transformed into a 0-point to 100-point scale for symptom severity and HRQoL subscales. Higher symptom scores indicate greater symptom severity, and higher HRQoL scores indicate better HRQoL.[4] The previous Fibristal CDR review included a study that assessed this measure as a reliable and responsive method. However, no minimal clinically important difference was reported.[4]

The clinical expert consulted on this review identified amenorrhea as a relevant clinical outcome that corresponds to a reduction in disease severity and progression. While the increase in fibroid size can influence the severity of the symptoms,[7] the effect of the fibroid on bleeding and pain depends on other factors beyond size alone.[8] No minimal clinically important difference was found in the literature regarding the size of the fibroid. However, Donnez 2016[2] assigned a reduction of 25% in the size of the fibroid as a clinically significant change.

Statistical Analysis

The authors calculated the need for 444 enrolled patients to achieve more than 85% power to detect a difference of 14% or more in the primary end point (percentage of patients in amenorrhea), assuming a dropout rate of around 10%. Descriptive statistics were provided for all outcomes in both groups using proportions in categorical outcome and means in continuous outcomes. The authors conducted comparative statistical analysis with the 10 mg control arm. However, the 10 mg arm cannot be considered an appropriate control comparison as it cannot provide any information regarding the efficacy of the approved 5 mg dose as compared with no treatment, placebo, or a practised active control. We present only the results of the 5 mg arm here.

Analysis Populations

Three main populations (FAS, the per-protocol set [PP], and the safety set) were defined for statistical analysis; FAS and PP had subpopulations based on the course of treatment:

1. FAS1 includes all randomized patients who received treatment at least once in the first treatment course.
2. FAS2 includes all randomized patients who received treatment at least once in the second treatment course.
3. FAS3 includes all randomized patients who received treatment at least once in the third treatment course.
4. FAS4 includes all randomized patients who received treatment at least once in the fourth treatment course.
5. PP includes all patients who completed the four courses with no major protocol violations.
6. PP4 includes all patients who received at least 56 days of treatment in the fourth course.
7. Safety set includes all patients who were randomized into the study and who received study medication at least once.

The primary efficacy analysis was conducted using the FAS1 population, with sensitivity analysis using the PP population. If fewer than four consecutive days of a bleeding pattern were missing, missing data were imputed using the greatest bleeding strength around the missing values. Observations for patients with four or more consecutive missing days of bleeding pattern assessment in the last 35 days of treatment cycle were not imputed and were considered missing, unless the patient had reported at least two days of spotting or at least one day of bleeding or heavy bleeding in the last 35 days of the treatment course, in which case the patient was deemed not in amenorrhea. Missing observations for patients who withdrew prior to completing the treatment course followed these rules:

- Amenorrhea assessment imputed as a failure if the primary reason for withdrawal was considered negative (e.g., adverse event [AE], lack of efficacy, protocol deviation).
- Amenorrhea assessment imputed as a success if the primary reason for withdrawal was considered positive (e.g., subject request, subject request and wished pregnancy, improvements that led to withdrawal).

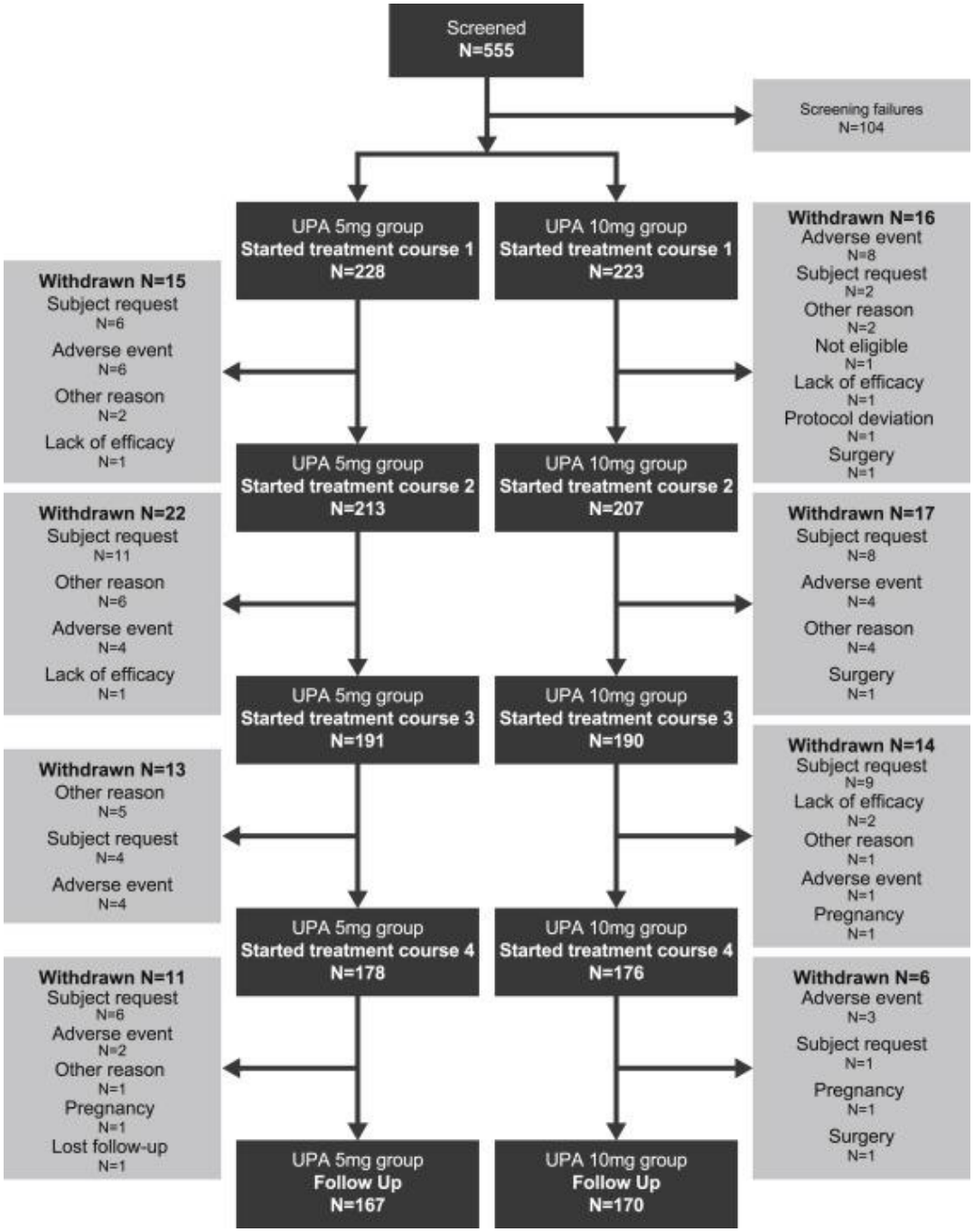
If the assessment remained missing after applying the aforementioned imputations, then missing data were excluded from any analysis. Sensitivity analyses were conducted to test the effect of different approaches to missing data imputation. These included the following:

- Assuming missing amenorrhea assessments as failures.
- Assuming missing amenorrhea assessments as successes.
- Allowing up to five missing consecutive days instead of three to impute the bleeding assessment.
- Conducting analysis using observed data only.

Patient Disposition

A total of 451 patients was randomized (228 patients to 5 mg of ulipristal acetate and 223 patients to 10 mg of ulipristal acetate). Overall, 61 patients (26.7%) withdrew from the 5 mg arm throughout the four treatment courses, and 53 (23.8%) withdrew from the 10 mg arm. Figure 2 provides a visual representation of patient disposition throughout the study. Table 4 provides the overall disposition throughout the study.

Figure 2: Flow Diagram of Patient Disposition



N = total number in the sample under study; UPA = ulipristal acetate.

Source: Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub. Used under Creative Commons licence CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[2]

Table 4: Total Patient Disposition

	PEARL IV	
	Ulipristal Acetate 5 mg	**Ulipristal Acetate 10 mg**
Screened, N	555	
Randomized, N	228	223
Discontinued, N (%)	61 (26.7)	53 (23.8)
FAS1, N[a]	195	185
PP4, N[a]	149	142
Safety set, N	230	221

FAS = full analysis set; N = total number in the sample under study; PP = per-protocol set.
[a] These numbers reflect the population used for primary analysis. Other outcomes may vary as no data imputation was conducted.
Source: Donnez et al. 2014,[5] Donnez et al. 2016.[2]

Exposure to Study Treatments

Evaluation of compliance was done through pill count and patients' diaries. The investigators of the PEARL IV presented a regimen compliance rate of 99.2% and stated that the usual drug-free interval for all patients was within the range of 51 to 56 days between treatment cycles.

Table 5: Exposure to Study Treatments

	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: PEARL IV manufacturer-provided clinical study report.[3]

Critical Appraisal

Internal Validity

A sufficient number of patients was recruited in PEARL IV to meet the power calculation. Patients were randomized to two doses of ulipristal acetate using a computer-based Web voice interaction system and were administered the intervention with matching placebo, thus insuring allocation concealment and maintenance of blinding. Study outcomes were predefined, and statistical analyses appropriately defined and conducted:

- descriptive analysis (proportions in categorical outcome and means in continuous outcomes)
- dose-comparative analyses (chi-square tests for binary end points with Newcombe–Wilson score method to calculate confidence intervals [CIs], Wilcoxon rank sum test with the Hodges–Lehmann estimator and corresponding Moses CI for the change in PBAC, and repeated-measures analysis of covariance for the total fibroid volume).

However, one of the main limitations that may affect the internal validity of the results is the trial's high attrition rate. More than 20% of the patients dropped out, mostly due to "subject request." Other patients who withdrew did so for a variety of reasons, including lack of efficacy, pregnancy, and AEs. Several sensitivity analyses were carried out to assess the impact of the missing data on the primary outcome.

External Validity

Based on input from the clinical expert consulted by CADTH, the PEARL IV inclusion and exclusion criteria were appropriate, and the baseline characteristics of the patients included in the study were similar to what is typically observed in practice. The lack of North American sites reduced the generalizability of the results to the Canadian population, considering that the clinical experience may point out that ulipristal acetate may not be as effective in patients of African descent. The outcomes described in this study (amenorrhea, fibroid size, PBAC, and USF-QoL) were considered by the clinical expert to be clinically relevant, and the PBAC and USF-QoL tools have been validated previously.

Two main limitations to the external validity of the study can be outlined as follows:

1. **Lack of appropriate comparators:** The 5 mg dose of ulipristal acetate was compared with the 10 mg dose of ulipristal acetate. The 10 mg dose is not approved by Health Canada for the treatment of uterine fibroids, and according to the clinical expert involved in the review, only the 5 mg dose would be used in Canada. As such, the focus of this review was on the 5 mg arm; therefore, only non-comparative descriptive results were available for the outcomes reported in this trial. Non-comparative descriptive results can no longer be used to assess causation, and cannot be used for statistical inference on efficacy or safety. In addition, the lack of comparative results from a randomized study introduces uncertainty regarding the effect of known or unknown confounders on the results. However, as presented in Appendix 6 and confirmed by the clinical expert, no current long-term medical treatment for uterine fibroids exists in practice. As such, no available active comparator can be used for comparison.
2. **In the PEARL IV study, patients received a maximum of four treatment courses with a three-month follow-up period:** The product monograph does not specify the number of courses. The current study provides results for four courses of treatment. There is no evidence of efficacy and tolerability for 5 mg of ulipristal acetate beyond four courses of three months' treatment each. In addition, the follow-up of three months after the last treatment course may be considered too short to assess long-term outcomes and the need for further treatment for uterine fibroids, including surgery.

Efficacy

Only those efficacy outcomes identified in the review protocol (see Appendix 1) are reported.

Amenorrhea

At the end of the study period, 95 patients out of 195 (48.7%) who have available data and received treatment in the first ulipristal acetate course achieved amenorrhea. Sensitivity analyses conducted for this population (FAS1) showed that when missing data were imputed as failures, then the proportion of patients who achieved amenorrhea was 41.7% (95 out of 228); when assuming all missing data are successes, then the proportion of patients who achieved amenorrhea was 49.1% (112 out of 228); when using imputation for patients with up to five consecutive missing days, the proportion of patients achieving

amenorrhea was similar to baseline (48.8%, 99 out of 203). Finally, when only using observed non-missing amenorrhea assessment, the proportion of patients who achieved amenorrhea was 60% (54 out of 90).

Out of 150 patients who received treatment in the fourth course and have available data, 94 (62.7%) reported amenorrhea. Based on the PP population in the first cycle, 75.8% of patients had amenorrhea; in the second cycle, 84.1% of patients; in the third cycle 86.4% of patients; and in the fourth cycle, 87.5% of patients.

Table 6: Proportion of Patients with Amenorrhea

	Ulipristal Acetate 5 mg (N = 228)
Primary End Point	
Amenorrhea at the end of all four treatment courses, n/N (%) (FAS1)[a]	95/195 (48.7%)
Amenorrhea at the end of all four treatment courses, n/N (%) (FAS4)	94/150 (62.7%)
Amenorrhea at the end of all four treatment courses, n/N (%) (PP4)[b]	94/149 (63.1%)
Secondary Amenorrhea End Points	
Amenorrhoea at the end of treatment course 1, n/N (%) (FAS1)	155/NR (71.8%)
Amenorrhoea at the end of treatment course 2, n/N (%) (FAS1)	152/NR (74.1%)
Amenorrhoea at the end of treatment course 3, n/N (%) (FAS1)	165/225 (73.3%)
Amenorrhoea at the end of treatment course 4, n/N (%) (FAS1)	158/227 (69.6%)
Amenorrhoea at the end of treatment course 1, n/N (%) (PP4)	125/165 (75.8%)
Amenorrhoea at the end of treatment course 2, n/N (%) (PP4)	132/157 (84.1%)
Amenorrhoea at the end of treatment course 3, n/N (%) (PP4)	152/176 (86.4%)
Amenorrhoea at the end of treatment course 4, n/N (%) (PP4)	154/176 (87.5%)

FAS = full analysis set; N = total number in the sample under study; n = number in a subgroup of the sample under study; NR = not reported; PP = per-protocol set.
[a] FAS1 includes all randomized patients who received treatment at least once in the first treatment course.
[b] PP4 includes all patients who received at least 56 days of treatment in the fourth treatment course.
Source: Table adapted from Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub. Used under Creative Commons licence CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International) CADTH does not own this work and permission should be sought from the copyright owner.[2]

Change in Bleeding Patterns

PBAC measurements were collected after screening and after treatment courses 1, 2, and 4. These show a gradual decrease of PBAC score with each subsequent treatment course, as detailed in Table 7.

Table 7: PBAC Scores

	Ulipristal Acetate 5 mg (FAS1 Unless Otherwise Specified, N = 228)
PBAC scores, first menses post-screening, baseline actual, mean (median)	300.2 (224.0)
PBAC scores, first menses post–treatment course 1, mean (median)	222.3 (122.5)
PBAC scores, first menses post–treatment course 2, mean (median)	167.6 (92.0)
PBAC scores, first menses post–treatment course 4, mean (median)	139.7 (77.5)

FAS1 = full analysis set 1; N = total number in the sample under study; PBAC = pictorial blood-loss assessment chart.
Source: Table adapted from Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub. Used under Creative Commons licence CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[2]

Volume of Three Largest Fibroids

The percentage change in the fibroid size at the first menses after treatment course 4 was a median of −67.0 (interquartile range [IQR] −85.6 to −35.1) in the FAS1 population. This result was identical in the PP4 population, where the percentage change was captured at a median of −67.0 (−85.6 to −35.1). Similarly, 78% of the patients were identified as having a fibroid reduction of 25% or greater in both FAS1 and PP4, while 63.8% of the patients were identified as having a fibroid reduction of 50% or greater in both analysis sets.

Table 8: Fibroid Size–Related Outcomes

Measure	Ulipristal Acetate 5 mg (FAS1 Unless Otherwise Specified, N = 228)
Fibroid Size: FAS1	
The total volume of 3 largest fibroids (cm^3), baseline actual, median (IQR)	42.6 (24.0 to 94.2)
After treatment course 1, PCFB, median (IQR)	−38.0 (−60.3 to −14.3)
End of treatment course 2, PCFB, median (IQR)	−54.1 (−74.6 to −33.0)
Post–first menses after treatment course 2, PCFB, median (IQR)	−53.6 (−76.8 to −23.6)
Post–first menses after treatment course 3, PCFB, median (IQR)	−60.8 (−76.3 to −25.5)
Post–first menses after treatment course 4, PCFB, median (IQR)	−67.0 (−85.6 to −35.1)
Fibroid Size: PP4	
Total volume of 3 largest fibroids (cm^3), baseline actual, median (IQR)	43.5 (24.0 to 91.7)
After treatment course 1, PCFB, median (IQR)	−39.4 (−60.3 to −15.2)
End of treatment course 2, PCFB, median (IQR)	−54.2 (−75.3 to −33.0)
Post–first menses after treatment course 2, PCFB, median (IQR)	−53.5 (−77.3 to −22.1)
Post–first menses after treatment course 3, PCFB, median (IQR)	−60.9 (−76.3 to −23.8)
End of treatment course 4, PCFB, median (IQR)	−71.8 (−87.6 to −32.6)
Post–first menses after treatment course 4, PCFB, median (IQR)	−67.0 (−85.6 to −35.1)
Follow-up, PCFB, median (IQR)	−65.0 (−85.1 to −28.4)
Fibroid volume reduction ≥ 25%	
Post–first menses after treatment course 1, n/N (%)	129/207 (62.3%)
Post–first menses after treatment course 2, n/N (%)	140/189 (74.1%)
Post–first menses after treatment course 3, n/N (%)	130/173 (75.1%)
Post–first menses after treatment course 4, n/N (%)	125/160 (78.1%)
Follow-up, n/N (%)	121/158 (76.6%)
Post–first menses after treatment course 1, n/N (%) (PP4)	110/168 (65.5%)
Post–first menses after treatment course 2, n/N (%) (PP4)	125/170 (73.5%)
Post–first menses after treatment course 3, n/N (%) (PP4)	124/166 (74.7%)
End of treatment course 4, n/N (%)	135/166 (81.3%)
Post–first menses after treatment course 4, n/N (%) (PP4)	125/160 (78.1%)
Follow-up, n/N (%) (PP4)	121/158 (76.6%)
Fibroid volume reduction ≥ 50%	
Post–first menses after treatment course 1, n/N (%)	77/207 (37.2%)
Post–first menses after treatment course 2, n/N (%)	101/189 (53.4%)
Post–first menses after treatment course 3, n/N (%)	107/173 (61.8%)
End of treatment course 4, n/N (%)	111/166 (66.9%)
Post–first menses after treatment course 4, n/N (%)	102/160 (63.8%)
Follow-up, n/N (%)	102/158 (64.6%)
Post–first menses after treatment course 1, n/N (%) (PP4)	66/168 (39.3%)
Post–first menses after treatment course 2, n/N (%) (PP4)	91/170 (53.5%)

Measure	Ulipristal Acetate 5 mg (FAS1 Unless Otherwise Specified, N = 228)
Post–first menses after treatment course 3, n/N (%) (PP4)	104/166 (62.7%)
End of treatment course 4, n/N (%) (PP4)	111/166 (66.9%)
Post–first menses after treatment course 4, n/N (%) (PP4)	102/160 (63.8%)
Follow-up, n/N (%) (PP4)	102/158 (64.6%)

FAS = full analysis set; IQR = interquartile range; N = total number in the sample under study; n = number in a subgroup of the sample under study; PCFB = percentage change from baseline; PP = per-protocol.
Source: Table adapted from Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub . Used under Creative Commons license CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International) CADTH does not own this work and permission should be sought from the copyright owner.[2]

Assessment of Pain Using a Visual Analogue Scale

Pain assessment results describe fluctuating levels of reported pain that decrease at the end of a treatment course and increase at the beginning of the subsequent course. This corresponds well with the cycles of the treatment-free periods in between courses. Table 9 provides the results of the change in pain from the baseline pain score.

Table 9: Assessment of Pain on a Visual Analogue Scale

	Ulipristal Acetate 5 mg (FAS1 Unless Otherwise Specified, N = 228)
Start of treatment course 1 (baseline), median (IQR)	39.0 (15.6 to 62.0)
End of treatment course 1, CFB median (IQR)	−24.5 (−51.0 to −2.0)
Start of treatment course 2, CFB median (IQR)	−3.0 (−23.6 to 8.5)
End of treatment course 2, CFB median (IQR)	−23.0 (−44.9 to 0.0)
Start of treatment course 3, CFB median (IQR)	−13.0 (−38.5 to 3.0)
End of treatment course 3, CFB median (IQR)	−20.5 (−49.1 to −3.6)
Start of treatment course 4, CFB median (IQR)	−14.5 (−39.0 to 1.0)
End of treatment course 4, CFB median (IQR)	−20.0 (−46.1 to −0.5)
After treatment course 4, CFB median (IQR)	−16.0 (−38.0 to 1.0)
Follow-up, CFB median (IQR)	−16.0 (−44.0 to 4.0)

FAS = full analysis set; IQR = interquartile range; N = total number in the sample under study; CFB = change from baseline.
Source: Table adapted from Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub. Used under Creative Commons licence CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[2]

Assessment of Quality of Life Using UFS-QoL

Similar to the pain assessment, the UFS-QoL tool identified a cyclic trend in the reduction from the baseline, where patients tend to bounce back closer to the baseline score in the treatment-free periods.

Table 10: Change From Baseline in UFS-QoL Score

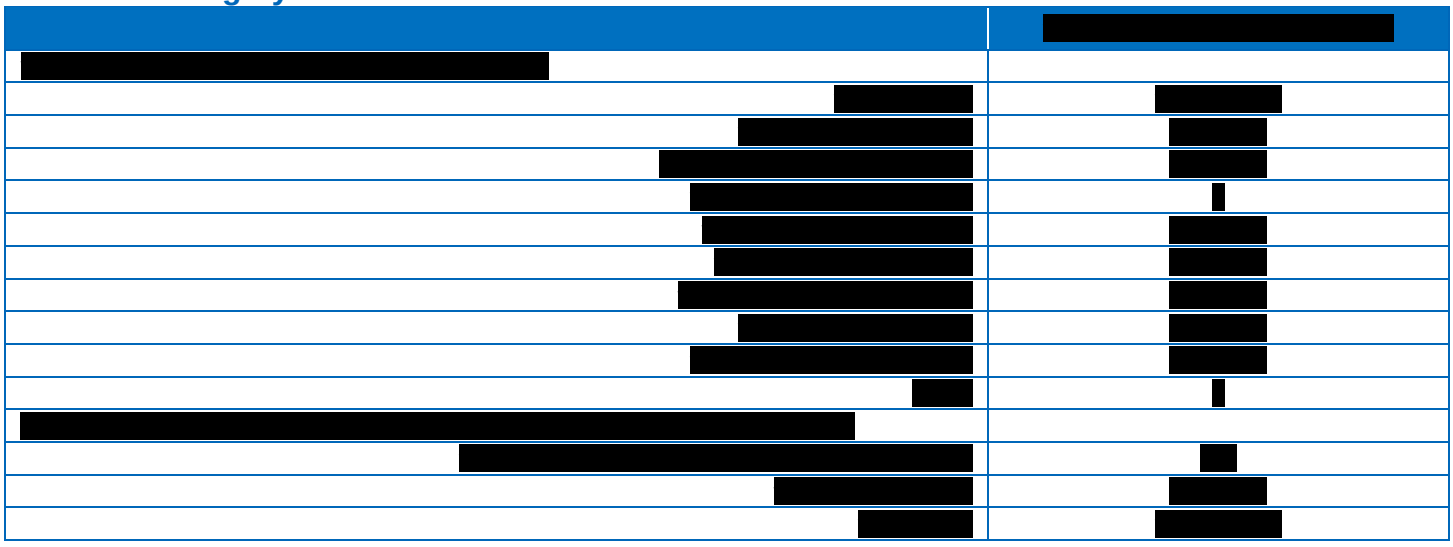
	Ulipristal Acetate 5 mg (FAS1 Unless Otherwise Specified, N = 228)
Start of treatment course 1 (baseline), median (IQR)	50.0 (37.5 to 62.5)
End of treatment course 1, CFB, median (IQR)	−34.5 (−46.9 to −18.8)
Start of treatment course 2, CFB, median (IQR)	−15.6 (−28.1 to 3.1)
End of treatment course 2, CFB, median (IQR)	−28.1 (−43.8 to −12.5)
Start of treatment course 3, CFB, median (IQR)	−15.6 (−31.3 to −6.25)
End of treatment course 3, CFB, median (IQR)	−28.1 (−46.9 to −15.6)
Start of treatment course 4, CFB, median (IQR)	−18.8 (−37.5 to −6.3)
End of treatment course 4, CFB, median (IQR)	−31.3 (−46.9 to −12.5)
After treatment course 4, CFB, median (IQR)	−21.9 (−40.6 to −9.4)
Follow-up, CFB, median (IQR)	−28.1 (−40.6 to −9.4)

FAS = full analysis set; IQR = interquartile range; N = total number in the sample under study; CFB = change from baseline.
Source: Table adapted from Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub. Used under Creative Commons licence CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.

Other Efficacy Outcomes

Only 9.1% of initially enrolled patients were planning to have surgery performed for the treatment of uterine fibroids. During the trial, surgery was performed in 3.1% of patients who were allocated to the 5 mg ulipristal acetate treatment arm.

Table 11: Surgery as an Outcome



Source: PEARL IV manufacturer-provided clinical study report.[3]

Harms

Details of the AEs recorded during the trial are presented in Table 12 as provided in Donnez 2016.[2] The safety profile of the long-term intermittent use of ulipristal acetate 5 mg did not show an overtly different safety profile from the original single-course use.

Table 12: Treatment-Emergent Adverse Events in PEARL IV

	Treatment Course 1			Treatment Course 2			Treatment Course 3			Treatment Course 4		
	UA 5 mg			UA 5 mg			UA 5 mg			UA 5 mg		
System Organ Class / PT	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
Number of Patients Receiving Study Medication		**230**			**215**			**193**			**180**	
At Least 1 On-Treatment TEAE	**233**	**102**	**44.3**	**114**	**59**	**27.4**	**44**	**32**	**16.6**	**58**	**43**	**23.9**
Reproductive System and Breast Disorders	**35**	**31**	**13.5**	**21**	**17**	**7.9**	**9**	**9**	**4.7**	**16**	**14**	**7.8**
Hot flush	14	13	5.7	9	8	3.7	3	3	1.6	5	5	2.8
Breast pain, tenderness, or discomfort	7	7	3.0	2	2	0.9	0	0	0.0	1	1	0.6
Pelvic pain	5	5	2.2	4	4	1.9	1	1	0.5	2	2	1.1
Infections and Infestations	**32**	**31**	**13.5**	**13**	**13**	**6.0**	**6**	**5**	**2.6**	**12**	**11**	**6.1**
Influenza	9	9	3.9	0	0	0.0	1	1	0.5	3	3	1.7
Nasopharyngitis	2	2	0.9	3	3	1.4	2	1	0.5	2	2	1.1
Nervous System Disorders	**37**	**30**	**13.0**	**19**	**16**	**7.4**	**5**	**4**	**2.1**	**6**	**6**	**3.3**
Headache	28	23	10.0	15	13	6.0	5	4	2.1	4	4	2.2
Gastrointestinal Disorders	**32**	**27**	**11.7**	**5**	**4**	**1.9**	**1**	**1**	**0.5**	**6**	**6**	**3.3**
Nausea	8	8	3.5	0	0	0.0	0	0	0.0	1	1	0.6
General Disorders and Administration Site Conditions	**10**	**10**	**4.3**	**8**	**6**	**2.8**	**2**	**2**	**1.0**	**2**	**2**	**1.1**
Fatigue	3	3	1.3	4	4	1.9	0	0	0.0	1	1	0.6
Blood and Lymphatic System Disorders	**9**	**9**	**3.9**	**0**	**0**	**0.0**	**1**	**1**	**0.5**	**0**	**0**	**0.0**
Anemia	6	6	2.6	0	0	0.0	0	0	0.0	0	0	0.0
Ear and Labyrinth Disorders	**7**	**7**	**3.0**	**2**	**2**	**0.9**	**0**	**0**	**0.0**	**0**	**0**	**0.0**
Vertigo	6	6	2.6	1	1	0.5	0	0	0.0	0	0	0.0

n = number of events; N = number of patients with event; PT = preferred term; TEAE = treatment-emergent adverse event; UA = ulipristal acetate.
Source: Table adapted from Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub. Used under Creative Commons licence CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[2]

Adverse Events

Most of the treatment-emergent AEs were reported during the first course of treatment, with 102 patients out of 230 (44.3%) reporting at least one AE in the 5 mg arm. Subsequently, this percentage is recorded at 27.4%, 16.6%, and 23.9% for treatment courses 2, 3, and 4, respectively. Headaches were the most commonly reported AE, followed closely by hot flushes, although both AEs followed the general trend of decreasing with subsequent treatment courses.

Serious Adverse Events

Of the 13 treatment-related serious AEs, nine were reported in the 5 mg ulipristal acetate arm. These were described as:

- five cases of menorrhagia
- one case of bipolar disorder
- one case of spontaneous myoma expulsion
- one case of abdominal pain
- one case of back pain.

Withdrawals Due to Adverse Events

Overall, 16 patients (7%) discontinued from the 5 mg treatment arm during the study due to AEs.

Mortality

[redacted].

Notable Harms

The authors did not report on any venous thromboembolism events that took place during the study. Endometrial hyperplasia was reported in three patients in the 5 mg arm, as well as twice in the 10 mg arm. An undefined endometrial malignant neoplasm was reported once in the 5 mg arm. It was later diagnosed as a case of endometrial adenocarcinoma and was believed to have been pre-existing.

Table 13: Neoplasm-Related Notable Harms

Notable Harms	Screening	After Treatment 2	After Treatment 4	Follow-up
	UA 5 mg (N = 230)	UA 5 mg (N = 193)	UA 5 mg (N = 168)	UA 5 mg (N = 164)
Endometrial hyperplasia, n (%)	0	1 (0.6)	1 (0.7)	1 (0.7)
Malignant neoplasm, n (%)	0	1 (0.6)	0	0
Endometrial adenocarcinoma, n (%)	0	1 (0.6) (same case as the malignant neoplasm)	0	0

N = total number in the sample under study; n = number in a subgroup of the sample under study; UA = ulipristal acetate.
Source: Table adapted from Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril.[Internet] 2016 Jan;105(1):165-173.e4. doi: 10.1016/j.fertnstert.2015.09.032. Epub 2015 Oct 23. Available from: http://www.sciencedirect.com/science/article/pii/S0015028215019603?via%3Dihub. Used under Creative Commons licence CC BY-NC-ND 4.0 (Attribution-NonCommercial-NoDerivatives 4.0 International). CADTH does not own this work and permission should be sought from the copyright owner.[2]

Place in Therapy[1]

Uterine fibroids tend to affect women of reproductive age.[9,10] Women with symptomatic uterine fibroids often experience heavy menstrual bleeding, pelvic pressure, and pain.[9,10] Choice of treatment for symptomatic fibroids is influenced by the symptom profile, desire for

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

future child-bearing, desire to retain uterus, menopausal status, and patient preference.[9] In cases where treatment is being considered, the benefits of symptom relief are balanced against potential risks of therapy.

Conventional treatment options have generally been invasive. These options have included hysterectomy, myomectomy, and uterine artery embolization.[9] For women who wish to preserve their child-bearing potential, treatment options have traditionally been limited to myomectomy.[9] Myomectomy is often presented as an alternative to hysterectomy for women with symptomatic fibroids. However, myomectomy via the abdominal or laparoscopic approach for subserosal or intramural fibroids carries greater surgical risk than hysterectomy due to a higher risk of blood loss and need for transfusion. Myomectomy may also compromise the integrity of the uterus and cause pelvic adhesions. As well, fibroids have an approximately 15% to 50% recurrence rate in women who have undergone myomectomy.[9] Further, for women with subserosal and intramural fibroids, the evidence does not support removal of fibroids for fertility.[10] Uterine artery embolization has also been investigated as an option for these women. However, it is associated with lower pregnancy rates, higher miscarriage rates, and more adverse pregnancy outcomes compared with myomectomy. Studies also suggest that uterine artery embolization is associated with loss of ovarian reserve.[10] As such, uterine artery embolization has limited utility in the treatment of women who wish to retain their uterus for child-bearing.

Gonadotropin-releasing hormone agonists (e.g., leuprolide acetate) may be used preoperatively to decrease fibroid size and increase patient hemoglobin. However, the long-term use of gonadotropin-releasing hormone agonists is generally not considered a treatment option for fibroids[9] and is generally precluded by the presence of menopausal symptoms and concerns regarding loss of bone mineral density. Occasionally, leuprolide acetate is used for the long-term treatment of severely debilitating chronic pelvic pain refractory to conventional treatment; however, women treated in this manner are essentially in menopause with associated risk of bone mineral density loss.

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 the more invasive options presented earlier. While initially investigated among women awaiting surgery,[2,11] more recent studies have reported the efficacy and safety of four repeated 12-week treatment courses of ulipristal acetate 5 mg or 10 mg daily.[12,13] These studies have provided the rationale for long-term use of ulipristal acetate beyond the four courses as currently reported in the literature; however, the number of treatment courses a patient receives would be based on individual physician clinical judgment. Patients who experience amenorrhea with this medication will generally become amenorrheic within two courses of treatment.[13] In women whose bleeding symptoms are not responsive to this medication after two courses, only a small incremental benefit is seen with further treatment.[13] Despite the potential application of long-term use of ulipristal acetate for women desiring future fertility, there is very limited evidence on the pregnancy outcomes for women who have been treated with ulipristal acetate. There is a need for more studies in this area.[14]

Discussion of Clinical Evidence as It Applies to the Request for Advice

Change in Patient Population

The 2013 CDEC recommendation for Fibristal was based on the Health Canada–approved indication at the time (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). The updated Health Canada–approved indication does not specify that patients must be eligible for surgery.[6] The evidence that was reviewed in 2013 (PEARL I and PEARL II), and on which the 2013 CDEC recommendation was based,[1] had eligibility of patients for surgery as a main inclusion criterion.[4]

One study (PEARL IV) met the selection criteria for this review. Evidence from the PEARL IV trial has shown that, after the first course of treatment, a slightly numerically lower proportion of patients in PEARL IV experienced amenorrhea (71.8%) compared with those reported in PEARL I (73.4%)[15] and PEARL II (75.3%).[16] It is worth noting, however, that patient characteristics in PEARL IV seem to indicate a less severe form of uterine fibroids than those present in PEARL I and PEARL II. Specifically, the median PBAC in the PEARL IV 5 mg arm is numerically lower than in PEARL I and PEARL II. In PEARL IV, it was 224 (IQR, 148 to 357) compared with 386 (IQR, 235 to 627) in PEARL I and 280 (IQR, 186 to 457) in PEARL II. PEARL IV also had a numerically smaller volume of the three largest uterine fibroids than in PEARL I and PEARL II. In PEARL IV, it was 42.6 cm^3 (IQR, 24.0 to 94.2) compared with 100.7 cm^3 (IQR, 40.0 to 205.3) in PEARL I and 78.2 cm^3 (IQR, 30.3 to 151.0) in PEARL II.[15,16] As such, any sort of comparison between the results of PEARL IV and those of PEARL I and PEARL II carries an inherent clinical heterogeneity. However, the clinical expert consulted on this review has identified these populations as sufficiently similar to what would be presented in practice.

The efficacy results from PEARL IV indicate that a large proportion of patients who achieve amenorrhea, reduction in fibroid size, and improvement in quality of life would surpass what is outlined in the natural course of the disease (see Appendix 6). For example, it is expected that only 3% to 7% of uterine fibroids would regress in size over time.[17,18] In the PEARL IV study, 76.6% of patients achieved a 25% or more reduction in fibroid size at the end of the follow-up. No major safety signals were reported in PEARL IV, and the safety profile was similar to what has been reported in PEARL I and PEARL II and, according to the clinical expert, to what has already been experienced so far in practice.

The input received from patient groups has identified patients who might not have been eligible for surgery as usually including anemic patients, patients suffering from obesity, and patients with bleeding abnormalities. These patients have experienced significant relief from long-term intermittent therapy with ulipristal acetate. In addition, as outlined in Subsection 4.2, Place in Therapy, there is an unmet need to be addressed in patients who wish to maintain fertility, are ineligible for surgery, wish to avoid surgery, or wish to reduce symptoms until reaching menopause. No available alternative medical therapy exists that can be administered in the long term and for which evidence suggests reduced fibroid size.

Changes in the Frequency of Treatment

The 2013 CDEC recommendation for ulipristal acetate was based on the Health Canada–approved indication at the time (i.e., with a duration of treatment limited to three months).

The updated Health Canada–approved indication allows for the use of 5 mg daily of ulipristal acetate as an intermittent treatment for uterine fibroids.[6] The previous 2013 CDEC recommendation stated that a condition of reimbursement be that the duration of treatment with ulipristal acetate should not exceed three months, specified as one three-month course of treatment with 5 mg of ulipristal acetate daily,[1] in line with the indication and the available evidence at the time (PEARL I and PEARL II).[4]

The results from the PEARL IV study provide descriptive non-comparative evidence of the efficacy and tolerability of 5 mg of ulipristal acetate over four courses of treatment. The treatment regimen used in the PEARL IV trial provided treatment for 12 weeks followed by a treatment-free period that extended to the start of the second menses. Across all reported outcomes, when considering the overall results using the PP population from each treatment course, we notice a trend in similar outcomes after each treatment course. However, when contrasting these results with the primary outcome using FAS1, we notice less favourable results. This indicates that the dropouts and missing data have moved the result in an unfavourable direction for 5 mg ulipristal acetate. The FAS results can provide a more conservative approach to the outcomes, where analysis of missing data indicates that in a worst-case scenario (all missing data are failures), 41.7% of patients achieved amenorrhea, while in a best-case scenario (all missing data are successes), 49.1% of patients achieved amenorrhea. The results of the main analysis support the notion of continued efficacy and tolerability of four intermittent courses of ulipristal acetate, due to:

- the proportion of patients who achieved amenorrhea after four courses of treatment (95 out of 195; 48.7%)
- a reduction in PBAC score from a mean of 300.2 at baseline down to a mean of 139.7
- a percentile change from baseline in median fibroid size of 67%
- the lack of strong signals of harm.

While no evidence is currently available for the efficacy and safety of 5 mg ulipristal acetate beyond four courses, in one single-arm open-label study (PEARL III), patients were administered 10 mg ulipristal acetate for up to eight consecutive courses.[19] The aim of the study was to describe changes in endometrial histology, laboratory parameters, and general safety.[19] The authors described that, out of 64 patients, all endometrial biopsies were benign, no abnormal laboratory results were captures, and no serious AEs were reported.[19] Considering that the intervention in PEARL III was of a different dose than the one approved by Health Canada, this study was not included in the CDR systematic review. In addition, the published descriptive results do not provide assessment of efficacy after four courses of treatment.[13,19]

In the absence of direct comparative evidence, the manufacturer submitted an indirect treatment comparison based [redacted] Please see Appendix 6 for a summary of the manufacturer-submitted indirect treatment comparison.

Economic Information

Summary of the Submitted Information

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 (Lupron).[20] Comparison with abdominal hysterectomy (with leuprolide acetate pre-surgical treatment) was provided as a scenario analysis. The Markov model simulated the proportion of women with controlled or uncontrolled bleeding during each monthly cycle. The model adopted a time horizon of 20 months with costs and quality-adjusted life-years (QALYs) discounted at a rate of 5% per annum. The analysis was conducted in women who reflect those recruited in the PEARL IV trial.[2,5]

For the regimen of four courses of ulipristal acetate, data on the probability of women having controlled bleeding after each course was obtained from the PEARL IV trial.[2,5] For the regimen of a single course of ulipristal acetate followed by leuprolide acetate, data on the probability of women having controlled bleeding during the course of ulipristal acetate were obtained from the PEARL IV trial and during treatment with leuprolide acetate from the PEARL II trial.[16] The probability of AEs (hot flashes) was derived from the PEARL II study for both regimens.

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 — the four courses both cost less ($4,606 versus $7,486) and were more effective (1.113 QALYs versus 1.109 QALYs). In the manufacturer's submission, the probability that the regimen of four courses was cost-effective given a threshold of $50,000 per QALY was 100%.

In the scenario analysis comparing four courses of ulipristal acetate to abdominal hysterectomy, the four courses cost less ($4,606 versus $12,015) and were less effective (1.113 QALYs versus 1.115 QALYs). The incremental cost per QALY gained for abdominal hysterectomy versus four courses of ulipristal acetate was $3.9 million per QALY, suggesting that abdominal hysterectomy is not cost-effective compared with four courses of ulipristal acetate.

Limitations of Manufacturer's Submission

CDR identified the following limitations with the manufacturer's analysis.

Choice of time horizon: The manufacturer's analysis restricts the time horizon to 20 months. This captures the four courses of ulipristal acetate treatment but excludes consideration of how patients will be managed after the 20-month time horizon. If a proportion of patients receiving ulipristal acetate eventually require abdominal hysterectomy, the likelihood of ulipristal acetate being cost-effective will diminish. Thus, a longer time horizon would be appropriate.

While the manufacturer's model does allow consideration of a longer time horizon, the structure considers that all patients would continue with ulipristal acetate beyond four courses of treatment with the assumption of continued efficacy, rather than that a proportion

of patients would move on to surgery. It is important to note that even with this assumption (which favours ulipristal acetate), as the time horizon increases, the cost-effectiveness of ulipristal acetate compared with hysterectomy decreases for four years, after which hysterectomy dominates ulipristal acetate (hysterectomy is associated with lower total costs and greater QALYs).

A further related limitation is that the manufacturer assumes the continued use of leuprolide acetate for the entire time horizon (in the comparator arm), despite the recommended six months of treatment.

Treatment failure and abdominal hysterectomy: The base-case analysis does not include the possibility for abdominal hysterectomy during the 20-month time horizon for either treatment arm. When adopting a longer time horizon, the analysis has the same limitation as mentioned under the limitation described above (choice of time horizon). The clinical expert consulted by CADTH viewed the assumption of no surgery during the 20-month time horizon as inaccurate and suggested that patients receiving ulipristal acetate who experienced no benefit after three months or limited benefits after the second course of treatment would move to surgery.

Consideration of available alternatives: The manufacturer compared four courses of ulipristal acetate to a single course of ulipristal acetate followed by leuprolide acetate. Comparison with abdominal hysterectomy (with pre-treatment with leuprolide acetate) was limited to a scenario analysis. 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 (i.e., women with moderate to severe signs and symptoms of uterine fibroids, of reproductive age, who are eligible for surgery). For the full population, four courses of ulipristal acetate should have been compared with a wider range of treatment options, including abdominal hysterectomy and embolization.

Further, to effectively capture the benefits of preserving the uterus, the model should have incorporated any utility benefit from this. Such a parameter should differ depending on whether the wish to preserve the uterus was in order to become pregnant versus other rationales.

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) would have been most pertinent. However, it was not feasible to consider in reanalysis given the design of the submitted model.

Lack of comparative data: There are no comparative studies comparing the effectiveness of four courses of ulipristal acetate with any of the comparators within the economic analysis. The only clinical trial identified for four courses of ulipristal acetate compares four courses at a 5 mg dose to four courses at a 10 mg dose.

The data used for the effectiveness of leuprolide acetate do not relate to the clinical context within the economic model. The clinical data relate to patients presenting with uterine fibroids while, for leuprolide acetate, the model relates to treatment after having been treated with ulipristal acetate.

Thus, any differences in clinical effectiveness between four courses of ulipristal acetate and a single course of ulipristal acetate followed by leuprolide acetate is speculative.

Follow-up post hysterectomy: The manufacturer's analysis suggests that patients would have repeated monthly clinic visits post hysterectomy. Justification for this assumption was not provided, and the clinical expert consulted by CDR did not support this. CDR assumed that such visits would end two months post hysterectomy.

CADTH Common Drug Review Reanalyses

CDR conducted a reanalysis that attempted to address some of the limitations detailed earlier; however, the model's design was not flexible enough to easily facilitate analysis incorporating the potential for surgery after treatment failure. As well, the reanalysis cannot address the limitations arising from the lack of comparative data.

The following changes to the model were adopted to partially address the limitations identified:

- For four courses of ulipristal acetate, it was assumed that 12.5% of women would require an abdominal hysterectomy after the four courses of treatment were complete (based on the rate of uncontrolled bleeding from the PEARL IV study). This percentage may be much higher, as the manufacturer assumed that the rate of controlled bleeding would tend to zero after treatment curtailment.
- A 40-month time horizon was adopted to incorporate the costs and benefits from subsequent surgery.
- Analysis conformed to CADTH economic guidelines21 — using both probabilistic analysis and a 1.5% discount rate.
- 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 (when deemed necessary).

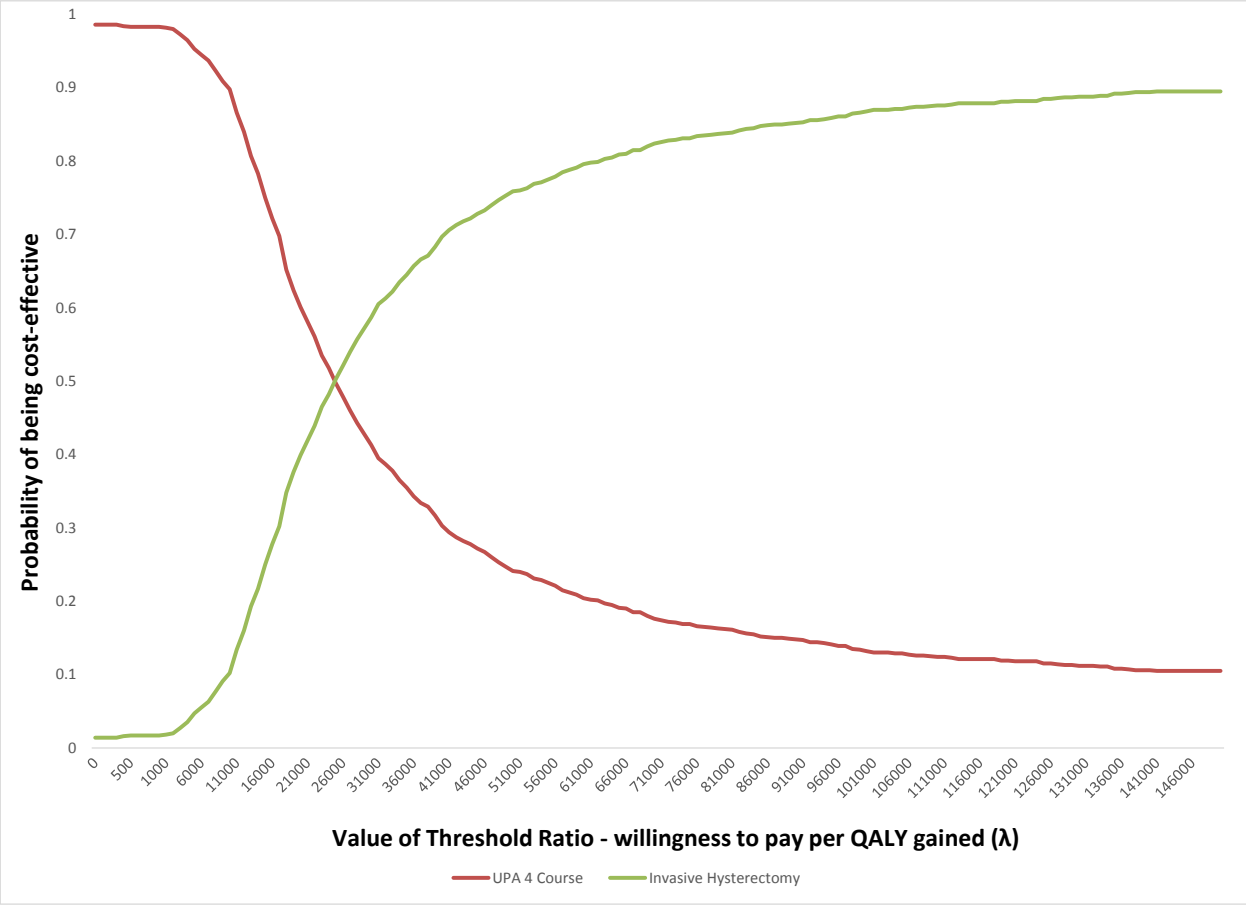
CDR reanalysis found six months of treatment with leuprolide acetate followed by abdominal hysterectomy to be more effective and more costly than four courses of ulipristal acetate, with an incremental cost per QALY gained of $25,158 (Table 2). If a decision-maker is willing to pay at least $25,158 per QALY gained, treatment with leuprolide acetate prior to hysterectomy is optimal. Based on a willingness to pay $50,000 per QALY, the probability that four courses of ulipristal acetate was cost-effective was 24.1% (see Figure 1). If a decision-maker is willing to pay less than $25,158 per QALY gained, intermittent treatment using ulipristal acetate is optimal.

Table 14: CADTH Reanalysis — Base Results

	QALYs	Cost	Incremental Cost per QALY Gained
Four courses of ulipristal acetate	2.028	$5,856	REF
Leuprolide acetate followed by abdominal hysterectomy	2.206	$10,328	$25,158

QALY = quality-adjusted life-year; REF = reference.

Figure 3: CADTH Reanalysis — Cost-Effectiveness Acceptability Curve



QALY = quality-adjusted life-year; UPA = ulipristal acetate.

Discussion of Economic Evidence

CDR was able to address some of the limitations identified with the manufacturer's economic submission, but the inflexibility of the submitted model, the lack of comparative data, and the lack of long-term data on the need for hysterectomy resulted in a CDR reanalysis that remains speculative.

Based on the reanalysis, CDR 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 $25,158 per QALY.

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).

Conclusions

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.
- 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.

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. CADTH received an RfA from the CDR-participating drug plans asking 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-centre, randomized, dose-controlled trial (PEARL IV, N = 451) in premenopausal women with uterine fibroids between 3 cm and 12 cm in diameter, inclusive, with heavy menstrual bleeding > 100 PBAC and uterine size < 16 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 three months, between which patients were off treatment.[2,3] The CDR review focused on the results of the 5 mg treatment arm, as this aligns with the Health Canada–approved indication. The efficacy results from PEARL IV indicated that 48.7% of patients (95 out of 195) achieved amenorrhea after four treatments; as well, patients experienced a reduction in PBAC score from a mean of 300.2 at baseline down to a mean of 139.7 and a 67% reduction in median

fibroid size from baseline.[2,3] No major safety signals were reported in PEARL IV; the safety profile was similar to what has been reported in PEARL I and II and, according to the clinical expert consulted for this review, 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 treatment comparison that was based [redacted].

Based on 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' 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 $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 a hysterectomy resulted in a CADTH reanalysis that remains speculative.

Appendix 1: Methodology

Objectives

To perform a systematic review of the beneficial and harmful effects of 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

An information specialist performed the literature search, using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the US National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Fibristal (ulipristal acetate).

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on June 30, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on October 18, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist: Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search, and Open Access Journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Review Methods

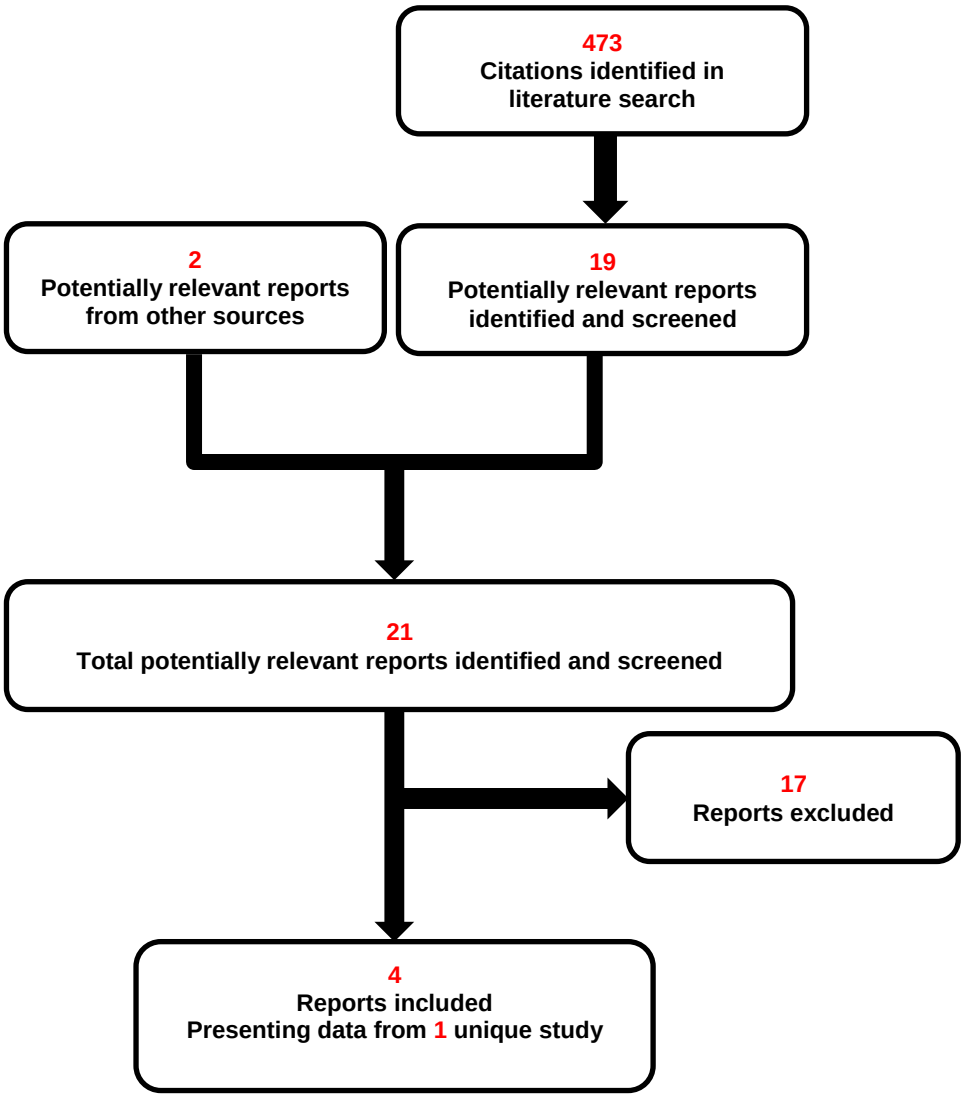
All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 15. Two CADTH Common Drug Review clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer 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. Excluded studies (with reasons) are presented in Appendix 5.

Table 15: Inclusion Criteria for the Systematic Review

Patient Population	Adult women of reproductive age with moderate to severe signs or symptoms from uterine fibroids	
Intervention	Repeated 3-month courses of UA 5 mg daily	
Comparators	**Medical** **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., laparotomic 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 event; GnRH = gonadotropin-releasing hormone; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PBAC = pictorial blood-loss assessment chart; RCT = randomized controlled trial; SAE = serious adverse event; UA = ulipristal acetate; VTE = venous thromboembolism; WDAE = withdrawal due to adverse event.

Figure 4: QUOROM Flow Diagram for Inclusion and Exclusion of Studies



Appendix 2: 2013 CADTH Canadian Drug Expert Committee Recommendation for Fibristal

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that ulipristal acetate 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:

Conditions:

- 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.

Reasons for the Recommendation:

1. In two double-blind randomized controlled trials (RCTs) ulipristal acetate was shown to be superior to placebo (PEARL I) and noninferior to leuprolide acetate (PEARL II) for decreasing menstrual bleeding in patients with uterine fibroids. In addition, ulipristal acetate was associated with fewer adverse events than leuprolide acetate in PEARL II.
2. At the submitted price, ulipristal acetate ($1,031 per three-month course) is less costly than leuprolide acetate ($1,042 per three-month course).

Of Note:

There were no data available in the included RCTs for patients with uterine fibroids who had previously been treated with gonadotropin-releasing hormone (GnRH) analogues.

Background:

Ulipristal acetate (ulipristal) 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. Ulipristal is available as 5 mg tablets and the recommended starting dose is 5 mg once daily initiated during the first seven days of menses and taken continuously for three months.

Summary of CDEC Considerations

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of ulipristal, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with uterine fibroids.

Patient Input Information

Two patient groups responded to the CDR call for patient input for this review. The patient groups stated the following:

- The pain, pressure, and often excessive blood loss resulting from uterine fibroids can exact a substantial toll on the quality of life and finances of those living with uterine fibroids.

- To date, few options outside of surgical intervention exist to treat uterine fibroids. Medical therapies, such as hormone treatments, administered preoperatively for short-term symptomatic relief while awaiting surgery, are often poorly tolerated; moreover, a woman's desire to preserve fertility may further limit the available treatment options.
- The patient groups stated that hysterectomy should not be considered the first (and in many cases the only) option that is offered to women living with uterine fibroids.

Clinical Trials

The systematic review included two 13-week, double-blind, RCTs. PEARL I was a placebo-controlled, superiority trial where participants (N = 242) were randomized (2:2:1) to ulipristal 5 mg once daily, ulipristal 10 mg once daily, or placebo. PEARL II was a noninferiority trial where participants were randomized (1:1:1) to ulipristal 5 mg once daily, ulipristal 10 mg once daily, or leuprolide acetate (leuprolide) 3.75 mg intramuscularly once monthly.

Outcomes

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

- Percentage of patients with a Pictorial Blood Assessment Chart (PBAC) score less than 75 at week 13.
- Changes in quality of life and symptoms — assessed using the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-HRQoL) Questionnaire; Measurement of Discomfort Due to Uterine Fibroids Questionnaire; and Short-Form McGill Pain Questionnaire.
- Changes in hematologic parameters — hemoglobin, hematocrit, and ferritin.
- Reversal of anemia (if present) — defined as the proportion of patients whose hemoglobin values increased to above 12 g/dL.
- Changes in myoma and uterine volumes.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The co-primary efficacy outcomes in PEARL I were the percentage of patients with a PBAC score less than 75 at 13 weeks and the change in total fibroid volume from screening to week 13. In PEARL II, the primary efficacy outcome was the percentage of patients with a reduction in uterine bleeding defined as a PBAC score less than 75 at the end of 13 weeks. Noninferiority of ulipristal compared with leuprolide was tested using a one-sided CI at a significance level of $P = 0.025$ against a –20% noninferiority margin.

Results

Based on the dosing recommended in the product monograph, CDEC focused its discussion on the results reported for the 5 mg once per day dose of ulipristal.

Efficacy

- The proportion of patients who achieved a PBAC score of less than 75 was 91.5% with ulipristal and 18.8% with placebo in PEARL I and 90.3% with ulipristal and 89.1% with leuprolide in PEARL II.
- The risk difference for achieving a PBAC score of less than 75 was reported as follows:
    - Ulipristal versus placebo: 72.7% (95% CI, 55.1% to 83.2%) in PEARL I.

  - Ulipristal versus leuprolide: 1.2% (95% lower confidence limit, –9.3%) in the per-protocol (PP) analysis and 1.0% (95% lower confidence limit, –9.4%) in the intention-to-treat (ITT) analysis in PEARL II; therefore, ulipristal was noninferior to leuprolide in both PP and ITT analyses.

- In PEARL I, there were statistically significant differences in both hemoglobin (mean difference 0.9 g/dL; 95% CI, 0.4 g/dL to 1.4 g/dL) and hematocrit (mean difference 2.6%; 95% CI, 1.0% to 4.1%) favouring ulipristal compared with placebo. In PEARL II, there were no statistically significant differences between ulipristal and leuprolide in hemoglobin, hematocrit, or ferritin.
- The proportion of patients whose hemoglobin values increased to more than 12 g/dL was 85.3% and 77.1% in the ulipristal and placebo groups (PEARL I) respectively, and 77.4% and 76.3% in the ulipristal and leuprolide groups (PEARL II) respectively.
- In PEARL I, there was a statistically significant reduction in total myoma volume favouring ulipristal compared with placebo (median difference –22.6%; 95% CI, –36.1% to –8.2%); however, the difference was not statistically significant when the data were log transformed.
- In PEARL II, there was no statistically significant difference between ulipristal and leuprolide on the log-transformed volume of the three largest myomas in the PP analysis; however, there was a statistically significant difference favouring leuprolide in the ITT analysis (mean difference 0.10; 95% CI, 0.01 to 0.19).
- Bleeding was controlled more rapidly with ulipristal compared with leuprolide in PEARL II ($P < 0.001$).
- There were no statistically significant differences in quality of life or symptom control between treatments in either PEARL I or PEARL II, with the exception of an improvement in the Measurement of Discomfort Due to Uterine Fibroids Questionnaire with ulipristal versus placebo in PEARL I (mean difference –4.0; 95% CI, –6.0 to –1.0).

Harms (Safety and Tolerability)

- Adverse events were more commonly reported in PEARL II than in PEARL I. The proportion of patients who experienced at least one adverse event was reported as follows:
  - In PEARL I, 49.5% in the ulipristal group and 45.8% in the placebo group.
  - In PEARL II, 77.3% in the ulipristal group and 84.2% in the leuprolide group.
- In PEARL II, hot flushes (25.8% versus 65.3%) and headache (25.8% versus 28.7%) were the most common adverse events, both of which occurred more frequently in patients treated with leuprolide than in those receiving ulipristal. However, no hormonal add-back therapy was administered during the trial to patients receiving leuprolide in order to mitigate the effects of estrogen deprivation, such as hot flushes and bone loss.
- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - In PEARL I, 2.1% in the ulipristal group and 4.2% in the placebo group.
  - In PEARL II, 5.2% in the ulipristal group and 4.0% in the leuprolide group.
- No withdrawals due to adverse events occurred in PEARL I. In PEARL II, one (1.0%) was recorded in the ulipristal group and five (5.0%) were recorded in the leuprolide group.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis, in women of reproductive age with moderate to severe symptoms of uterine fibroids who would be eligible for surgery,

comparing ulipristal with leuprolide, with the base case from the health care system perspective. The analysis was conducted using a decision tree with four possible outcomes: controlled bleeding with and without hot flashes and uncontrolled bleeding with and without hot flashes. Efficacy data were derived from PEARL II. Three cost elements were included in the analysis: drug costs, other medical costs, and lost productivity. Utility values for each health state were obtained through a Web-based survey using health state descriptors and the EQ-5D questionnaire. The time horizon for the analysis was 90 days, which reflects the standard course of treatment. The manufacturer found ulipristal dominates leuprolide, as it was less expensive ($1,280 compared with $1,365) and more effective (0.177 compared with 0.165; quality-adjusted life-year [QALY] gains of 0.012) during a 90-day time horizon.

The major limitations within the model were related to the utility values adopted, particularly for uncontrolled bleeding, oral administration, and bleeding control with ulipristal and leuprolide. The limitations overestimated the QALY gain from ulipristal versus leuprolide. However, reanalysis using more conservative assumptions led to the same conclusions as the manufacturer's base-case analysis — ulipristal remained dominant compared with leuprolide — QALY gains of 0.004 and cost savings of $85 for ulipristal.

At the submitted price of $11.46 per 5 mg tablet, the three-month cost of ulipristal is $1,031. Leuprolide, delivered through a 3.75 mg intramuscular injection on a monthly basis for three months, is $1,042 per three-month course.

Other Discussion Points:

- Ulipristal is the only medication 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.
- There were no North American centres included in the PEARL I or PEARL II trials.
- Participants in the PEARL I and PEARL II trials were predominantly Caucasian (approximately 85%); therefore, minorities were underrepresented in these trials. CDEC noted that black women are disproportionately affected by uterine fibroids, but only represented a small percentage of the study populations (0% in PEARL I and 9% in PEARL II).
- Ulipristal is administered orally and leuprolide is administered as an intramuscular injection. The relative ease of oral administration may lead to an expanded use of ulipristal relative to leuprolide.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no data available to assess the impact of treatment with ulipristal on surgical outcomes.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

October 16, 2013 Meeting

Regrets:

None

Conflicts of Interest:

One CDEC member did not vote on the recommendation.

About This Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

Appendix 3: Patient Input

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

1. Brief Description of Patient Groups Supplying Input

Two patient groups provided input on this review: the Women's Health Initiative Network and Canadian Women with Fibroids Limited. The Women's Network is a national, non-profit organization dedicated to providing awareness and education, creating policy change, influencing patient engagement, and facilitating consumer research in all areas of women's health, including uterine, vaginal, sexual, and bladder health. A description of Canadian Women with Fibroids was not provided in its submitted report.

The patient input submission from the Women's Network was prepared by internal staff. However, external sources, namely a consumer survey by Epsilon, was used as an information source, and James F. McGrath was consulted for statistical analyses. Potential conflicts of interest included funding received from Tyros Biopharma and Allergan Inc. in the $0 to $5,000 range and in the $10,000 to $50,000 range, respectively.

No conflict of interest declarations were reported.

2. Condition-Related Information

The Women's Health Initiative Network gathered information from a national consumer survey involving 1,117 English-speaking and French-speaking patients and consulted three physicians and two registered nurses. A March 2017 Canadian Women with Fibroids survey conducted among women with fibroids was used for the preparation of the that group's submission. The majority of participants in this survey indicated their preference to retain their uterus (76%), avoid hysterectomy (63%), and minimize clinical symptoms during the six-month to nine-month recovery time following hysterectomy.

Fibroids are benign tumours of the uterus. They occur mostly among women between the ages of 30 and 50, and they affect productivity in these women's lives by interfering with their career and starting or maintaining a family. Fibroids result in a plethora of symptoms, which can be classified as urogenital (heavy menstrual bleeding, prolonged periods, pelvic pressure or pain, frequent urination, urgency, difficulty emptying the bladder), circulatory (fatigue and anemia due to heavy blood clots), fertility-related (infertility, pregnancy loss, preterm birth), other clinical symptoms (constipation, backache, leg pains, bloating), and a general lack of everyday functions (caring for children, work, exercise, socializing, intercourse, insomnia, depression, and chronic pain). Of these, most women rated menstrual bleeding and pain as the most important symptoms to be controlled.

3. Current Therapy-Related Information

Treatment of uterine fibroids can be medicinal or surgical in nature, although full satisfaction from symptom relief without losing fertility is seldom achieved. Medications are targeted to regulating the menstrual cycle, thereby minimizing heavy bleeding and pelvic pressure instead of eliminating fibroids (although shrinkage is sometimes possible). Gonadotropin-releasing hormone agonists, for example, act by blocking the production of estrogen and progesterone and are used to shrink fibroid size prior to surgery. However, significant hot

flashes and bone loss with long-term use limit its use to no more than three to six months. Progestin-releasing intrauterine devices provide relief from heavy bleeding without affecting fibroid size or number or preventing pregnancy. Tranexamic acid and oral contraceptives or progestins are also used to control heavy bleeding; common side effects with these agents are weight gain, bloating, headaches, and nausea. Nonsteroidal anti-inflammatory drugs can provide pain relief but have no impact on bleeding.

Among surgical treatment options, magnetic resonance imaging–guided focused ultrasound surgery is a non-invasive procedure that preserves the uterus. Examples of this procedure vary in mode of action, effectiveness, and side effects. Uterine artery embolization involves the injection of small particles (embolic agents) into the uterine arteries, limiting blood supply to the fibroids and causing shrinkage and subsequent symptom reduction. Myolysis is a laparoscopic procedure that destroys fibroids and supplies blood vessels through the use of radiofrequency energy, electric current, or laser. Laparoscopic or robotic myomectomy can only be performed in cases where few fibroids exist. In cases where there are a large number of fibroids, myomectomy — a more invasive procedure — needs to be performed. Myomectomy can cause uterine scarring and interfere with fertility. Submucosal fibroids present inside the uterus can be surgically removed by hysteroscopic myomectomy. This stops bleeding but other symptoms persist. Finally, hysterectomy is the permanent removal of the uterus, but it is often associated with long wait times. While satisfactory outcomes are typically seen among those women who opt for hysterectomy, it comes at the expense of exposure to surgical risk and permanently losing the ability to bear children. This limits its preference among women. Furthermore, hospitalization, long recovery times, bleeding and infection, the inability to work and socialize, and concomitant hormonal therapies were frequently reported as limitations by survey responders. Other commonly cited limitations of surgery were high costs and having to take pain medications for an extended period of time.

4. Expectations About the Drug Being Reviewed

The need for conservative treatment options that provide bleeding control and avoid surgery is unanimously expected from new therapies. Major symptoms that patients want to be controlled include vaginal bleeding, pain, and bulking (bloating, abdominal pressure). Conservative or bridging treatments that are easy to administer, can be taken while waiting for surgery, or avoid surgery and associated complications altogether are also preferred.

Women in the 2017 consumer survey who were on ulipristal acetate stated that their quality of life was good (50%), very good (37.5%), and excellent (12.5%). Patients also experienced the elimination of vaginal bleeding, reduction in the size of fibroids, and decreased pain or an end to pain altogether. Participants who were on ulipristal acetate intermittently indicated that the wait time for hysterectomy was long and uncertain. Those suffering from severe anemia therefore had additional concerns about surgery. Using ulipristal acetate over a longer period had stabilized their hemoglobin status to safer levels during their wait period for surgery. Many patients were able to delay and sometimes forego hysterectomy by taking ulipristal acetate over long periods until menopause, when fibroids reduce in number and size naturally. The relative efficacy and safety of ulipristal acetate compared with other therapies also meant that patients could maintain a healthy lifestyle and satisfactory quality of life through exercise, socializing, and being able to work. However, the overwhelming reason why patients chose ulipristal acetate over surgery was to retain the functional state of their uterus in order to preserve fertility.

Appendix 4: Excluded Studies

Study and RefID	Reason for Exclusion
Ferrero et al. 2015 [22]	Design
Donnez et al. 2013 [23]	Design
Briggs 2013 [24]	Intervention
Wilhelmi 2012 [25]	Article in German
Levens and Nieman 2008 [26]	Design
Fauser et al. 2017 [19]	Intervention
Seitz et al. 2017 [27]	Intervention
Jesam et al. 2016 [28]	Design
Kalampokas et al. 2016 [29]	Design
Bizzarri et al. 2015 [12]	Design
Donnez et al. 2014 [13]	Intervention
Nieman et al. 2011 [30]	Intervention
Williams et al. 2012 [31]	Intervention
Donnez et al. 2012 [16]	Intervention
Donnez et al. 2012 [15]	Intervention
Warner et al. 2010 [32]	Intervention
Fiscella and Eisinger 2008 [33]	Design

RefID = reference identification number.

Appendix 5: Clinical Features, Epidemiology, and Natural History of Uterine Fibroids

Objective

The objective of this appendix is to provide an overview of the clinical features, epidemiology, and natural history of uterine fibroids.

Overview

Uterine fibroids (leiomyomas or myomas) are benign monoclonal tumours arising in reproductive-age women that form from the smooth muscle cells of the myometrium.[8] The etiology and early pathogenesis of uterine fibroids are not fully understood.[34] However, hormonal influence plays a major role in the formation and growth of uterine fibroids.[35] Small uterine fibroids are asymptomatic and require no medical treatment.[7] However, as the disease progresses, symptoms may appear that directly interfere with a patient's life and cause significant morbidity.[7] These symptoms are directly related to the size, number, and location of the fibroids and can be categorized into three categories of symptoms.

- **Excessive menstrual bleeding:** Heavy or prolonged bleeding during menses is considered the most common fibroid symptom and may lead to anemia and social difficulties.[36] In one survey study, 29% of patients with uterine fibroids reported "severe/very severe" heavy or prolonged menstrual bleeding, 30% reported "mild/moderate," and 41% reported "none in the last three months."[7]
- **Symptoms related to the bulk size of the uterine fibroid:** Pelvic pain or pressure, bowel or urinary obstruction, and venous compression are all caused by the bulky and large size of uterine fibroids.[7,37] In a national survey study, 24% of patients with uterine fibroid reported severe or very severe abdominal pain, 50% reported mild to moderate **pain, and only 26% had no pain in the past three months.**[7]
- **Infertility and other reproductive and pregnancy complications:** Submucosal and intramural uterine fibroids have been associated with decreased fertility outcomes[38] and a higher risk of spontaneous pregnancy loss.[39]

The proportion of women who progress from asymptomatic uterine fibroids to symptomatic is unclear, nor is it clear whether all women necessarily progress. The clinical expert consulted for this review indicated that uterine fibroids would rarely regress on their own. The symptoms that each patient manifests may vary considerably, as symptoms are related to the size, location, and number of uterine fibroids. Nonetheless, it is believed that up to half of all uterine fibroids are symptomatic.[9,40,41] The exact prevalence and incidence of uterine fibroids are hard to determine, as many cases go undiagnosed due to the lack of symptoms. However, an estimated prevalence of 70% to 80% in women 50 years of age and older has been reported in a survey study in the US.[42] Additionally, a longitudinal study reported an incidence of 8.9 per 1,000 woman-years among white women and an incidence of 30.6 per 1,000 woman-years among black women.[43] In Canada, one study published in 2014 screened 11,880 women and found that 12.0% had a diagnosis of uterine fibroids.[44] Another survey published in 2016 of 9,413 reproductive-age Canadian women reported physician-diagnosed uterine fibroids in 4.1% of respondents.[45] A third survey published in 2012 indicated that 5.5% of a sample of 2,514 Canadian women reported the occurrence of uterine fibroids.[46]

For women with symptomatic uterine fibroids, management is largely determined by the severity of symptoms and whether the patient wishes to maintain fertility.[9] The definitive treatment option is hysterectomy.[9] An underlying indication of uterine fibroids accounts for

just over one-third (35%) of the 47,000 hysterectomies that were performed in Canada in 2008-2009.[47] For women who wish to preserve their fertility options, only myomectomy is a valid intervention. Current available medical treatment aims to control symptoms and to reduce the size of fibroids in preparation for surgical or radiological interventions. Table 16 outlines currently available modalities of treatment.[4] However, with the exception of the updated indication of ulipristal acetate, any treatment that provides long-term relief is invasive in nature.

Table 16: Currently Available Treatments for Uterine Fibroids[4,48,49]

Treatment Method	Description or Options	
Conservative ("watchful waiting")	No medical or surgical intervention in place. Patient has scheduled follow-up to discuss symptoms or signs and imaging to follow fibroid size.	
Medical	***Non-hormonal medications*** • Tranexamic acid (**b**) • Anti-inflammatories (**b/p**) ***Hormonal medications*** • Combined hormonal contraception (**b**) • Progestin only (**b**)	• Progestin intrauterine system (**b**) • GnRH agonists (**b/p**) • Danazol (**b/p**) • Selective progesterone receptor modulators (UA) (**b/p**) ***Experimental usage*** • Aromatase inhibitors **(b/p)**
Interventional	Uterine artery embolization (**b/p**) Infertility therapy (i.e., in vitro fertilization) (**i**)	***Options not widely available*** MRI-guided focused ultrasound (**b/p**)
Surgical	Hysterectomy (**b/p**) Myomectomy (**b/p/i**) Endometrial ablation (**b**)	***Options not widely available*** • Uterine artery occlusion **(b/p)** • Myolysis **(b/p)**

b = treatment to address menstrual bleeding; GnRH = gonadotropin-releasing hormone; i = treatment to assist infertility; MRI = magnetic resonance imaging; p = treatment to relieve pressure or pain symptoms; UA = ulipristal acetate.
Note: None of these therapies, with the exception of the ulipristal acetate updated indication, is indicated for long-term use.

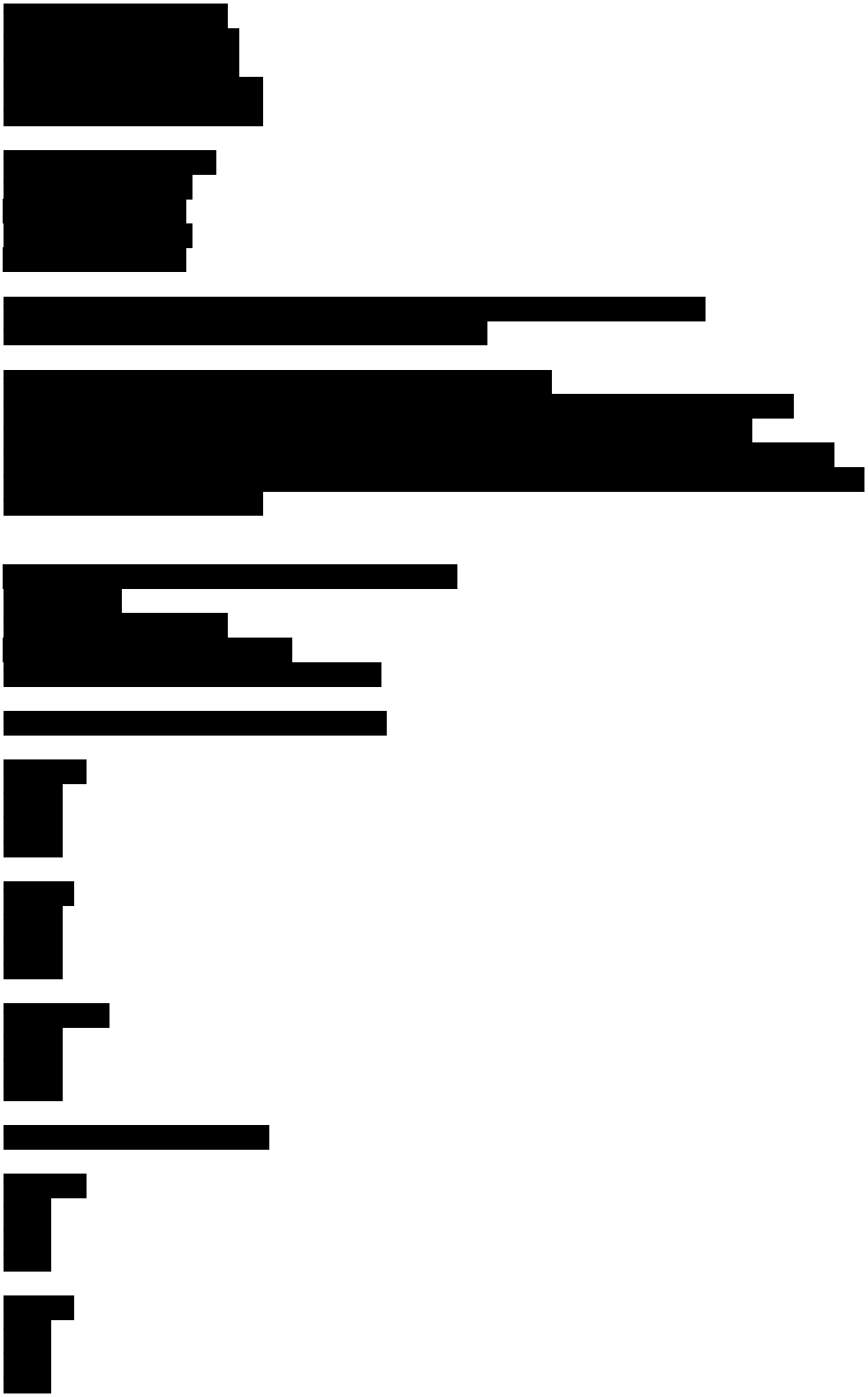
Source: CADTH Common Drug Review, Ulipristal acetate (Fibristal).[4]

Two longitudinal imaging studies have shown that, if left untreated, a small percentage of fibroids (3% to 7%) will regress over three to six years; the rate of growth can vary considerably between patients and between fibroids within the same patient.[17,18] Uterine fibroids seem to shrink following childbirth. This has been demonstrated by the fact that uterine fibroids will naturally regress after menopause and, as such, would require no treatment.[9]

Summary

Uterine fibroids are a common benign tumour in reproductive-age women that can lead to considerable morbidity and impact quality of life. Not all uterine fibroids require treatment but, for those that do, there is a general lack of long-term non-invasive treatment.

Appendix 6: Summary and Critical Appraisal of Manufacturer-Submitted Extrapolation and Indirect Comparison



Appendix 7: Cost Comparison

The comparators presented in Table 17 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 17: CDR Cost Comparison Table for Drugs Used for Uterine Fibroids

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average 90-Day Drug Cost ($)
Ulipristal acetate (Fibristal)	**5 mg**	**Tablet**	**11.4600**	**5 mg daily for 3 months**	**11.46**	**1,031**
Treatments not specifically indicated but used for the management of symptoms of uterine fibroids						
Buserelin acetate (Suprefact)	1 mg/mL	10 mL nasal spray	82.9900	200 mcg in each nostril 3 times daily for up to 6 to 9 months	9.96	896
Goserelin acetate (Zoladex)	3.6 mg	Injection	422.6778	Once every 28 days	15.10	1,359
	10.8 mg		1,204.7322	Once every 13 weeks	13.24	1,191
Leuprolide acetate (Lupron depot)	3.75 mg	Injection	359.3300	Once monthly for up to 6 months	11.57	1,078
	11.25 mg		1,070.6100	Once every 3 months for up to 6 months	11.49	1,071
Nafarelin acetate (Synarel)	2 mg/mL	8 mL nasal spray	374.0600[a]	200 mcg twice daily for up to 6 months	9.35	872
Triptorelin pamoate (Trelstar)	3.75 mg	Injection	346.3100	Once every 28 days for up to 6 months	12.36	1,113

CDR = CADTH Common Drug Review.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed July 2017)[50] unless otherwise indicated and do not include dispensing fees.

[a] Saskatchewan Formulary (July 2017).[51]

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