Common Drug Review

Clinical Review Report

December 2013

Drug	ulipristal acetate (Fibristal) (5 mg tablets)
Indication	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 three months.
Listing request	As per indication
Manufacturer	Actavis Specialty Pharmaceuticals

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ABBREVIATIONS

AE	adverse event
CDR	Common Drug Review
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
DB	double blind
E2	estradiol
FDA	Food and Drug Administration
FTG	fibroid treatment group
GnRH	gonadotropin-releasing hormone
Hgb	hemoglobin
Hct	hematocrit
HRQoL	health-related quality of life
ITT	intention-to-treat
LA	leuprolide acetate
LCL	lower confidence limit
LOCF	last observation carried forward
MBL	menstrual blood loss
MCID	minimal clinically importance difference
MRI	magnetic resonance imaging
NCG	normal control group
NSAID	nonsteroidal antiinflammatory drug
PAP	Papanicolaou test (pap test)
PBAC	pictorial bleeding assessment chart
PP	per-protocol
PRM	progesterone receptor modulator
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SFMPQ	Short-form McGill Pain Questionnaire
SPRM	selective progesterone receptor modulator
UA	ulipristal acetate
UF	uterine fibroids
UFE	uterine fibroid embolization
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire
US	ultrasound
VAS	visual analogue scale
VTE	venous thromboembolism
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Uterine fibroids, leiomyomas, or myomas are benign tumours characterized by excessive or irregular uterine bleeding (with or without anemia), pelvic pressure, or pain, which may compromise fertility; however, many women may be asymptomatic.[1] Uterine fibroids, the risk for which rises with age until menopause, represents one of the most common reasons for women to seek gynecological care and is the leading indication for hysterectomy.[1] Uterine fibroids are reported to affect about 35 million reproductive-aged women in the US, with a global prevalence ranging between 20% and 77%.[1]

The management of uterine fibroids includes "watchful waiting," medical, interventional, and surgical options.[1-3] Hysterectomy is the definitive treatment for uterine fibroids; however, alternative uterine-sparing surgical or minimally invasive procedures include myomectomy, uterine artery embolization, or endometrial ablation.[1,4] The choice of surgical procedure is guided by patient age and the desire to preserve fertility or avoid hysterectomy.[1,3]

Although surgery is the treatment of choice for uterine fibroids, various drugs have been used for symptom management during the preoperative period.[1-3,5] They include hormonal therapies (i.e., gonadotropin-releasing hormone [GnRH] agonists, combined hormonal contraceptives, progestin-releasing intrauterine systems, progestins, danazol, aromatase inhibitors) and non-hormonal therapies (i.e., nonsteroidal antiinflammatory [NSAID] drugs, antifibrinolytics [tranexamic acid]).[2,3,5] None of the listed drugs has a Health Canada Notice of Compliance (with or without conditions) for the treatment of uterine fibroids. GnRH agonists are preferred agents in clinical practice for shrinking fibroid size and controlling or stopping bleeding, which may restore hemoglobin levels,[1,6,7] enable less invasive surgical procedures to be used,[1,6] and mitigate intraoperative blood loss.[7] However, GnRH agonists are associated with important adverse effects, particularly menopause-related symptoms and reduced bone mineral density, which limit long-term use of these drugs.[1]

Ulipristal acetate (Fibristal) is an oral hormonal therapy 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. Reimbursement is being sought by the manufacturer in accordance with the indication. Through its antiproliferative and apoptotic effects, respectively, ulipristal potentially controls uterine bleeding[1] and shrinks the size of fibroids.[5]

The objective of this systematic review was to evaluate the beneficial and harmful effects of ulipristal acetate 5 mg for the treatment of the signs or symptoms due to uterine fibroids in adult women of reproductive age who are eligible for surgical intervention.

Results and Interpretation

Included Studies

The evidence for this review was drawn from two phase III (PEARL I, n = 144; and PEARL II, n = 204) double-blind, randomized controlled trials (RCTs), comprising 348 adult women of reproductive age with moderate to severe signs or symptoms due to uterine fibroids, who are eligible for surgical intervention. PEARL I was a placebo-controlled trial, while PEARL II was a non-inferiority, double-dummy trial with a GnRH agonist (leuprolide) as the active comparator. Both trials included a 10 mg ulipristal arm, which was not evaluated for this review, as the 10 mg dose is not a Health Canada-approved dose; the systematic review assessed the results for the approved ulipristal 5 mg dose. Inclusion and exclusion

criteria were generally comparable between trials, with the exception of anemia, which was a specific inclusion criterion in PEARL I, but not PEARL II. For both trials, the primary efficacy outcome was the percentage of patients with a reduction in uterine bleeding as determined by a pictorial bleeding assessment chart (PBAC) score < 75 at 13 weeks; PEARL I also considered the change in total fibroid volume from screening to week 13 as a co-primary efficacy outcome. Both trials were designed as 13-week trials, following which study medication was stopped and planned surgical intervention was then completed, switched, or cancelled at the discretion of each site's clinical investigator; only exploratory efficacy outcomes were available for the post-treatment period, which ran for up to an additional six months (i.e., 38 weeks in total). Neither trial included patients from North America. Black patients, who are disproportionately affected by uterine fibroids, were not studied in PEARL I owing to a failure in recruitment; by comparison, black patients comprised less than 10% of the study population in PEARL II. A large proportion of surgeries were not completed as planned; however, no information was provided on the reasons for cancelling these surgeries.

Efficacy

The systematic review protocol, in consideration of patient input submitted, identified quality of life and symptom control as key efficacy outcomes; however, no statistically significant between-group differences were identified on these outcomes in either trial, except improved scores on the yet-to-be-validated Measurement of Discomfort Due to Uterine Fibroids Questionnaire among ulipristal-treated patients versus placebo in PEARL I. The primary efficacy outcome for both PEARL I and II was the percentage of patients with a PBAC score < 75 at week 13, which was how the trials defined a reduction in uterine bleeding. In PEARL I, a greater proportion of patients treated with ulipristal (91.5%) compared with placebo (18.8%) achieved a PBAC score < 75 at week 13 (difference: 72.7%; 95% confidence interval [CI], 55.1% to 83.2%). In PEARL II, the proportion of patients who achieved a PBAC score < 75 at week 13 was not statistically significantly different between ulipristal (90.3%) and leuprolide (89.1%) groups in the primary (per-protocol [PP]) analysis (difference: 1.2%; 95% lower confidence limit [LCL], –9.3%), or in the intention-to-treat (ITT) analysis (difference: 1.0%; 95% LCL, –9.4%). Hence, ulipristal was found to be non-inferior to leuprolide based on the pre-specified non-inferiority margin of –20% in PEARL II. Although the PBAC is a validated instrument for assessing uterine blood loss, it becomes less well correlated with menstrual blood loss with higher volumes of blood loss.[8] Given that the women enrolled in the trials were determined to have levels of menorrhagia well above the PBAC threshold for menorrhagia (i.e., > 100), it is unclear to what extent observed changes in PBAC scores, especially changes in higher scores, correlate with changes in blood loss, let alone those occurring as a function of treatment. Nonetheless, control of bleeding (PBAC < 75) was achieved in $\geq$ 90% of ulipristal-treated patients in both trials at week 13. It is also uncertain how well ulipristal compares with other hormonal and non-hormonal therapies, as no other comparative trials were identified from the literature.

Harms

There were no deaths reported in either trial. Adverse events (AEs) were more common overall in PEARL II than in PEARL I. In PEARL I, headache (4.2% versus 4.2%) and constipation (4.2% versus 2.1%) were the most common AEs overall in ulipristal-treated compared with placebo-treated patients, respectively. In PEARL II, hot flashes (25.8% versus 65.3%) and headache (25.8% versus 28.7%) were the most common AEs, both of which occurred more frequently in leuprolide-treated patients than in those receiving ulipristal. Of note, no hormonal add-back therapy was administered during the trial to leuprolide-treated patients in order to mitigate the effects of estrogen deprivation, such as hot flashes and bone loss; the Society of Obstetricians and Gynaecologists of Canada[9] recommends the use of add-back hormonal therapy whenever GnRH agonists are used in the treatment of endometriosis, a common comorbid condition in uterine fibroids, according to the consulting clinical expert. However, based on

discussion with the clinical expert involved in the review, opinion is mixed in the setting of uterine fibroids; most clinicians would likely opt to treat with a GnRH agonist alone for a period not exceeding six months. Also notable is the differential frequency of hot flashes that occurred between PEARL I and II in ulipristal-treated patients: in PEARL I, the frequency was less than 3%, while in PEARL II, it was 25.8% despite one of the purported advantages of ulipristal therapy being avoidance of adverse effects arising from estrogen deprivation from GnRH agonist therapy. According to the manufacturer, patients in PEARL I were not provided with adverse effect information about the risk of hot flashes from treatment, which may partly explain the lower frequency of hot flashes observed in the ulipristal group in PEARL I compared with PEARL II.

Serious adverse events (SAEs) were infrequent overall and similar between ulipristal and comparator groups in both PEARL I (2.1% versus 4.2%, respectively) and PEARL II (5.2% versus 4.0%, respectively), with no particular pattern of concentration. The same was true for withdrawals due to adverse events (WDAEs): no WDAEs occurred in PEARL I, while in PEARL II, one (1.0%) was recorded in the ulipristal group and five (5.0%) were recorded in the leuprolide group. Venous thromboembolism (VTE) and endometrial hyperplasia or carcinoma were pre-specified as important harms for the systematic review. There were no reports of VTE in either PEARL I or II. In PEARL I, there were no diagnoses of endometrial hyperplasia or malignant neoplasm at the end of the treatment period (i.e., at week 13),[10] while in PEARL II, there was one diagnosis of hyperplasia of a simple, non-atypical nature at week 13.[11] In the six months (i.e., up to week 38) following treatment cessation, investigators did not identify any malignant endometrial changes in either trial and indicated that a majority of patients had experienced a reversal of initial, non-physiologic endometrial changes after stopping treatment.[10,11]

Other Considerations

Based on discussion with the clinical expert involved in the review, the following potential off-label uses of ulipristal were identified.

Emergency Contraception

The medication is in a class of drugs that have been used in different therapeutic areas, including emergency contraception. However, this indication is available outside Canada and the corresponding dose is six times higher (30 mg ulipristal acetate) than the daily dose approved for uterine fibroids. Given this and the availability of less expensive and easier to obtain alternatives for emergency contraception in Canada, the clinical expert felt ulipristal was unlikely to be used as emergency contraception.

Heavy Menstrual Bleeding

Ulipristal might be used for the control of acute heavy menstrual bleeding. However, the clinical expert thought this too was unlikely — at least in the near future — unless the post-market experience confirms this among Canadian providers.

Conclusions

In two phase III RCTs, 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 agonist (i.e., leuprolide) therapy in PEARL II; hence, ulipristal was found to be non-inferior to leuprolide based on the pre-specified non-inferiority 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 and SAEs. 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 are 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 compared with placebo on validated quality of life instruments — quality of life was identified as a patient-important outcome for this review.

Summary of the Pharmacoeconomic Submission

Background

The manufacturer compares ulipristal acetate (UA) to leuprolide acetate (LA) in women of reproductive age with moderate to severe symptoms of uterine fibroids (UFs) who would be eligible for surgery. UA is given as an oral medication at 5 mg per day for up to 90 days. The manufacturer submitted UA at a confidential price of $11.46 per 5 mg tablet for a 3 month cost of $1,031. Alternatively, LA is delivered through a 3.75 mg intramuscular injection on a monthly basis for three months ($1,042 per three-month course).

Summary of Economic Analysis

The manufacturer conducted a cost-utility analysis with the base case from the health care system perspective. The target population is as per the Health Canada indication — women of reproductive age with moderate to severe symptoms of UF who would be eligible for surgery. The analysis was conducted through the use of 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 the PEARL II clinical trial. Three cost elements were included in the study: 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 instrument. The time horizon for the analysis was set at 90 days, which reflects the standard course of treatment.

Results of Manufacturer's Analysis

UA is found to be less expensive than LA ($1,279.92 compared with $1,365.02; a cost savings of $85.10) and more effective (0.177 compared with 0.165; quality-adjusted life-year [QALY] gains of 0.012) during a 90-day time horizon. Thus, UA dominates LA.

Interpretations and Key Limitations

The major limitations within the model related to the utility values adopted, particularly for uncontrolled bleeding, for oral administration and for bleeding control with UA and LA. The limitations overestimated the QALY gain from UA versus LA. However, reanalysis using more conservative assumptions led to the same conclusions as the manufacturer's base analysis.

Results of Common Drug Review Analysis

Reanalysis found UA to be dominant compared with LA: QALY gains of 0.004 and cost savings of $85.33 for UA.

Issues for Consideration

UA is the only licensed product for the treatment of women of reproductive age with moderate to severe symptoms of UF who would be eligible for surgery.

Conclusion

Both the manufacturer's base result and the Common Drug Review (CDR) reanalysis suggest that UA is more effective and less costly compared with LA.

TABLE 1: SUMMARY OF RESULTS

Outcome		PEARL I		PEARL II	
		UA 5 mg	PB	UA 5 mg	LA 3.75 mg
QUALITY OF LIFE/SYMPTOM CONTROL					
***UFS-QoL**, change from baseline to week 13*					
Symptom severity score,[a] LS mean (SD)		NR	NR	–28.2 (23.1)	–27.2 (22.9)
Difference (95% CI)		NR		–1.0 (–10.4 to 8.4)	
HRQoL total score[a]		NR	NR	20.3 (24.1)	17.8 (23.3)
Difference (95% CI)		NR		2.5 (–7.3 to 12.3)	
Measurement of Discomfort due to UF, change from baseline to week 13					
Median (min, max)		–9.0 (–22.0 to 5.0)	–6.0, (–24.0 to 11.0)	NR	NR
Difference (95% CI)		–4.0 (–6.0, –1.0)		NR	
SFMPQ, change from baseline to week 13					
A (SFMPQ),[b] median (min, max)		–5.0 (–33.0 to 15.8)	–2.5 (–26.0 to 11.0)	–5.0 (–38.0 to 17.0)	–5.5 (–40.0 to 9.6)
Difference (95% CI)		–2.0 (–4.0 to 0.0)		0.2 (–2.0 to 3.0)	
B (VAS),[b] median (min, max)		–30.0 (–120.0, to 62.0)	–16.5 (–89.0 to 44.0)	–31.0 (–100.0 to 29.0)	–32.0 (–100.0 to 27.0)
Difference (95% CI)		–12.0 (–25.0 to 1.0)		4.0 (–5.0 to 14.0)	
C (PPI),[b] median (min, max)		–1.0 (–4.0 to 1.0)	–1.0 (–3.0 to 1.0)	–1.0 (–4.0 to 2.0)	–1.0 (–4.0 to 3.0)
Difference (95% CI)		0.0 (0.0 to 1.0)		0.0 (–1.0 to 0.0)	
CONTROL OF BLEEDING					
% of patients who achieved PBAC score < 75 at week 13, % (n/N); difference (95% CI)	ITT	91.5 (86/94)	18.8 (9/48)	89.8 (88/98)	88.8 (87/98)
		72.7 (55.1 to 83.2)		1.0 (–9.4[c])	
	PP	92.9 (79/85)	20.0 (9/45)	90.3 (84/93)	89.1 (82/92)
		72.9 (54.6 to 83.8)		1.2 (–9.3[c])	
% of patients in amenorrhea at week 13, % (n/N)		73.4 (69/94)	6.3 (3/48)	75.3 (70/93)	80.4 (74/92)
Difference (95% CI)		67.2 (50.2 to 77.0)		–5.2 (–18.7, 8.6)	
Time to achievement of amenorrhea (i.e., PBAC ≤ 2), median days (95% CI)[12d]		NR	NR	8 (6 to 15)	23 (14 to 28)
SURGICAL					
Number of patients *not* proceeding to surgery after treatment, n (%)		61 (64.2)	35 (72.9)	52 (55.9)	50 (53.8)
Number of patients switched to less invasive surgeries, n (%)		65 (69.9)	37 (77.1)	57 (62.0)	55 (59.1)

Outcome	PEARL I		PEARL II	
	UA 5 mg	PB	UA 5 mg	LA 3.75 mg
DISCONTINUED				
Discontinued study, n (%)	7 (7.3)	3 (6.3)	5 (4.9)	6 (5.9)
SAEs				
Subjects with ≥ 1 SAEs, n (%)	2 (2.1)	2 (4.2)	5 (5.2)	4 (4.0)
WDAEs				
WDAEs, n (%)	0	0	1 (1.0)	5 (5.0)
NOTABLE HARMS				
VTE	NR	NR	NR	NR
Endometrial hyperplasia	0	0	1 (1.0%)	0
Endometrial carcinoma	0	0	0	0

CI = confidence interval; HRQoL = health-related quality of life; ITT = intention-to-treat analysis; LA = leuprolide acetate; LS = least square; n = subpopulation; N = population; NR = not reported; PB = placebo; PBAC = pictorial bleeding assessment chart; PP = per-protocol analysis; PPI = present pain intensity; SAE = serious adverse event; SD = standard deviation; SFMPQ = Short-form McGill Pain Questionnaire; UA = ulipristal acetate; UF = uterine fibroids; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire; VAS = visual analogue scale; VTE = venous thromboembolism; WDAE = withdrawal due to adverse event.

Note: The 10 mg group was not presented as it is not a Health Canada-approved dose for UA.

[a]Adjusted least squares mean.

[b]Median.

[c]Lower confidence limit; a value greater than the pre-specified non-inferiority margin of –20% demonstrates non-inferiority.[11]

[d]Exploratory analysis; no formal statistical testing performed.[12]

Unless otherwise specified, efficacy data for PEARL I are presented using the ITT analysis set, while data for PEARL II are presented using the PP analysis set.

Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

1. INTRODUCTION

1.1 Disease Prevalence and/or Incidence

Uterine fibroids (UFs), leiomyomas, or myomas are benign tumours characterized by excessive or irregular uterine bleeding, which may lead to the development of anemia, pelvic pressure or pain, increased urinary frequency or constipation, and possibly compromised fertility.[1] UFs represent one of the most common reasons for women to seek gynecological care. Nonetheless, many women with UFs are asymptomatic, such that diagnosed UFs are thought to represent only half of all cases.[1,5]

UFs are reported to affect about 35 million reproductive-aged women in the US and are twice as prevalent in black women than in other racial or ethnic populations.[1] Rising with age until menopause, the global prevalence of UFs is estimated to range between 20% and 77%.[1]

1.2 Standards of Therapy

Canadian clinical practice guidelines are currently being updated; previous ones were published in 2003 by the Society of Obstetricians and Gynaecologists of Canada.[3] Based on discussion with the clinical expert involved in the review, key considerations in the management of patients with UFs include the following:

- Determine the presenting complaint and impact on quality of life (i.e., heavy menstrual bleeding versus infertility).
- Determine patient's general health status (i.e., is patient anemic).
- Determine if patient wishes fertility- or uterine-sparing options versus definitive treatment options, such as hysterectomy.
- Characterize fibroid location, size, and quantity using examination and imaging techniques.

The management of UFs includes "watchful waiting," medical, interventional, and surgical options (Table 2).[1-3] Hysterectomy is the definitive treatment for UFs;[1-3] fibroids represent the most common reason for hysterectomy in Canada.[13] Other uterine-sparing surgical or minimally invasive procedures — including myomectomy, uterine artery embolization, or endometrial ablation — are available as alternative treatment options in women wishing to preserve fertility.[1-4] The choice of surgical procedure is guided by patient age and the desire to preserve fertility or avoid hysterectomy.[1,3] Without definitive surgery (i.e., hysterectomy), there remains a risk of relapse following successful surgical or interventional procedure.[1]

Although surgery is the treatment of choice for UFs, a variety of drugs have been used — with varying degrees of success — for symptom management during the preoperative period.[1-3,5] They include hormonal therapies (i.e., gonadotropin-releasing hormone [GnRH] agonists, combined hormonal contraceptives, progestin-releasing intrauterine systems, progestins, danazol, aromatase inhibitors) and non-hormonal therapies (i.e., nonsteroidal antiinflammatory [NSAID] drugs, antifibrinolytics [tranexamic acid]).[2,3,5] Although a hormonal treatment option, the use of danazol has fallen out of favour owing to issues of tolerability and safety.[9] None of the listed drugs has a Health Canada Notice of Compliance (with or without conditions) for the treatment of UFs. GnRH agonists (primarily leuprolide acetate) are preferred agents in clinical practice for shrinking fibroid size and controlling or stopping bleeding, which may also restore hemoglobin levels,[1,6,7] enable less invasive surgical procedures to be used,[1,6] and mitigate intraoperative blood loss.[7] Fibroid size may be reduced by 35% to 65% within three months of treatment with this medical therapy.[2] However, adverse effects (e.g., hot flashes) related to the class's hypoestrogenic mechanism of action may limit tolerability; in addition, safety concerns about bone

mineral density limit GnRH agonist treatment to short-term use only.[1] All other medications, as described in Table 2, aim to treat specific symptoms, such as menstrual bleeding or signs such as infertility.

TABLE 2: UTERINE FIBROID TREATMENT — GENERAL APPROACHES

Treatment Method	Description and/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**) Antiinflammatories (**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**) ***Not widely available options***: MRI-guided focused ultrasound (**b/p**)
Surgical	Hysterectomy (**b/p**) Myomectomy (**b/p/i**) Endometrial ablation (**b**) ***Not widely available options***: Uterine artery occlusion (**b/p**) Myolysis (**b/p**)

b = treatment to assist menstrual bleeding; i = treatment to assist infertility; GnRH = gonadotropin-releasing hormone; MRI = magnetic resonance imaging; p = treatment to assist pressure or pain symptoms; UA = ulipristal acetate.
Sources: Society of Obstetricians and Gynaecologists of Canada (SOGC)[3] and American College of Obstetricians and Gynecologists.[2]

1.3 Drug

Ulipristal acetate (UA) (Fibristal) has a Health Canada indication for the treatment of moderate to severe signs and symptoms of UFs in adult women of reproductive age who are eligible for surgery. The duration of treatment is limited to three months.[14] An oral tablet formulation, ulipristal is a selective progesterone receptor modulator (SPRM) that has been shown to exhibit agonist, antagonist, or mixed agonist and antagonist activity in endo- and myometrial tissue.[1,5,15] Antiproliferative effects on endometrial tissue reduce or eliminate uterine bleeding.[1] Through its antiproliferative and apoptotic effects, ulipristal reduces the size of UFs.[5] Despite inhibition of ovulation, ulipristal is reported to have

low affinity for androgen and no affinity for estradiol or mineralocorticoid receptors.[1,5] UA initially gained market access (outside of Canada) through its approval as an emergency contraceptive.[15]

Ulipristal — for the treatment of UFs — is dosed orally once daily as a 5 mg tablet initiated during the first seven days of menses and taken continuously for three months. It is taken without regard to food.[14]

Indication under review
Treatment of moderate to severe signs and symptoms of UFs in adult women of reproductive age who are eligible for surgery. The duration of treatment is limited to three months.
Listing criteria requested by sponsor
As per indication

TABLE 3: KEY CHARACTERISTICS OF ULIPRISTAL ACETATE AND LEUPROLIDE ACETATE

	Ulipristal Acetate	Leuprolide Acetate
Mechanism of action	SPRM characterized by a tissue-specific, partial progesterone antagonist effect, direct effect on endometrium and fibroids thorough inhibition of cell proliferation and apoptosis	Synthetic nonapeptide analogue of naturally occurring GnRH that inhibits gonadotropin production; acts specifically on pituitary gonadotrophs
Indication[a]	Treatment of moderate to severe signs and symptoms of UFs in adult women of reproductive age who are eligible for surgery; duration of treatment is limited to 3 months	Treatment of endometriosis, for pain relief and reduction of endometriosis lesions, for a period of 6 months
Route of administration	Oral	Intramuscular injection
Recommended dose	5 mg orally once daily for 3 months continuously	3.75 mcg injected intramuscularly monthly[a]
Serious side effects or safety issues	**SAEs:** The frequency was low (2.1% to 5.2%) and without particular pattern in the PEARL I and II trials.[10,11] **Warnings:** Do not use with concomitant use of contraceptive pill or progestogen-releasing IUD; in patients with mild to severe hepatic impairment, or in patients with severe uncontrolled asthma **Contraindications:** In women who are or may become pregnant, patients with undiagnosed abnormal vaginal bleeding, patients with uterine, cervical, ovarian, breast cancer	**SAEs:** Potential for interstitial lung disease **Warnings:** Reports of convulsions, isolated cases of short-term worsening of signs and symptoms, condition worsening may require discontinuation or surgery **Contraindications:** In women who are or may become pregnant, or in patients with undiagnosed abnormal vaginal bleeding
Other	None	Not indicated for women > 65 years old

GnRH = gonadotropin-releasing hormone; IUD = intrauterine device; SAE = serious adverse event; SPRM = selective progesterone receptor modulator; UF = uterine fibroids.
[a]Health Canada indication.
[b] Leuprolide acetate is indicated in the treatment of endometriosis for a period of six months.[16]
Sources: Ulipristal acetate product monograph[14] and leuprolide acetate product monograph.[16]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of UA 5 mg for the treatment of the signs or symptoms due to UFs in adult women of reproductive age who are eligible for surgical intervention.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 4.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

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

No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. See APPENDIX 2: LITERATURE SEARCH STRATEGY for the detailed search strategy.

The initial search was completed on June 4, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on October 16, 2013. 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 Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters). See APPENDIX 2: LITERATURE SEARCH STRATEGY for more information on the grey literature search strategy. 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.

Two CDR 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 discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult women of reproductive age with moderate to severe signs or symptoms from UFs, who are eligible for surgical intervention Subpopulations: Race or ethnicity	
Intervention	UA 5 mg daily	
Comparators	**Medical:** *Hormonal:* GnRH agonists Combined hormonal contraceptives Progestin-releasing intrauterine system Progestins *Other:* Placebo Watchful waiting	*Non-hormonal:* Tranexamic acid NSAIDs
	Surgical: Hysterectomy Myomectomy Uterine artery occlusion Myolysis	**Non-surgical:** Uterine artery embolization MRI-focused ultrasound
Outcomes	***Key efficacy outcomes:*** Quality of life by validated instrument Symptom control (i.e., pain or discomfort) ***Other efficacy outcomes:*** Number (%) of patients *not* proceeding to surgery after treatment Number (%) of invasive surgeries (i.e., laparotomic hysterectomy) avoided Control of bleeding • Hematin alkaline test (menstrual blood loss) • PBAC (menstrual blood loss) • Time to control bleeding • Amenorrhea 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; Hct = hematocrit; Hgb = hemoglobin; MRI = magnetic resonance imaging; NSAID = nonsteroidal antiinflammatory drug; PBAC = pictorial bleeding assessment chart; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse events; UA = ulipristal acetate; UF = uterine fibroids; VTE = venous thromboembolism.

3. RESULTS

3.1 Findings from the Literature

A total of 196 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

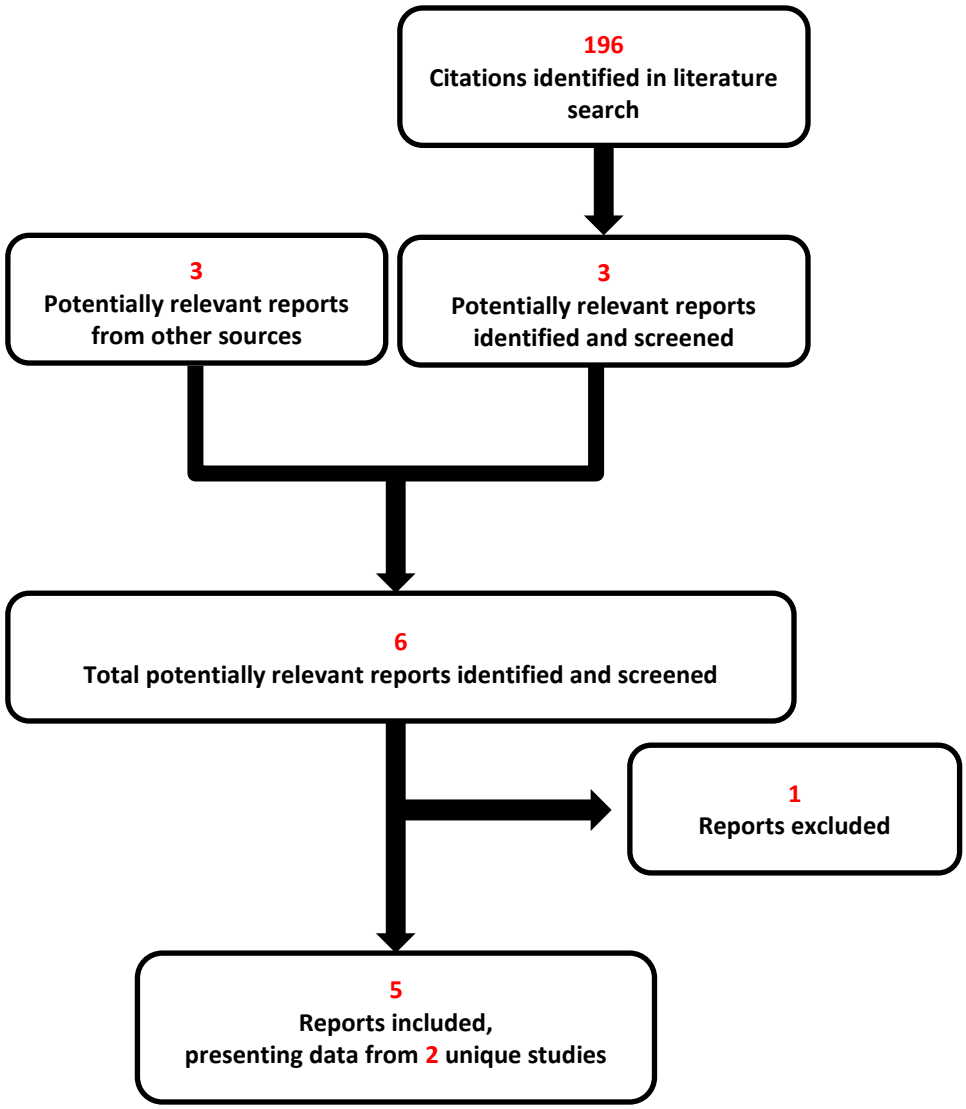

TABLE 5: DETAILS OF INCLUDED STUDIES

		PEARL I	PEARL II
DESIGNS AND POPULATIONS	**Study design**	Multicentre, double-blind, placebo-controlled RCT stratified by screening hematocrit (≤ 28% or > 28%) and race (black or other)	Multicentre, double-blind, double-dummy, active comparator-controlled RCT stratified by race (black or other)
	Locations	Czech Republic, Hungary, India, Romania, Russia, Ukraine	Austria, Belgium, Germany, Spain, Israel, Italy, Poland
	Randomized (N)	N = 242	N = 292
	Inclusion criteria	Premenopausal women; aged 18 to 50 years; BMI ≥ 18 and ≤ 40; PBAC score > 100 during day 1–8 of menses prior to baseline visit; myomatous uterus volume ≤ 16 weeks; ≥1 uterine myoma size of ≥ 3 cm and ≤ 10 cm in diameter, diagnosed by US; eligible for hysterectomy, myomectomy, UAE, or endometrium ablation within 13 and ≤ 14 weeks from baseline; unremarkable clinical breast exam at screening; unremarkable PAP test within past 12 months or at screening; use of non-hormonal method of contraception if of child-bearing years	
		Myoma-related anemia defined as Hgb ≤10.2 g/dL; absence of macrocytic anemia	
	Exclusion criteria	History of uterus surgery (except Caesarean section or cervical conisation), endometrial ablation, or UAE; history of or current uterine, cervical, ovarian, or breast cancer; history of atypical hyperplasia or current endometrium hyperplasia or similar lesions in screening biopsy or in biopsy performed within past 6 months; known hemoglobinopathy or severe coagulation disorder; large uterine polyp (> 2 cm); ≥ 1 ovarian cysts ≥ 4 cm in diameter diagnosed by US; history of or current treatment for myoma with SPRM or GnRH agonist; treatments with progestins or OC, ASA, mefenamic acid, anticoagulants, antifibrinolytics, systemic glucocorticoids; abnormal hepatic function; pregnant or lactating	
		Endometrial adenocarcinoma Any metallic, ferromagnetic, or electronic implant and/or device that may interfere with MRI exam or potentially pose a risk in orbit	History of or current osteoporosis
DRUGS	**Intervention**	UA 5 mg or 10 mg orally once daily x ≤ 13 weeks	UA 5 mg or 10 mg orally once daily x 12–13 weeks
	Comparator(s)	Placebo	Leuprolide 3.75 mg i.m.
DURATION	Run-in	5–8 weeks[a]	
	Double-blind	13 weeks[b]	
	Follow-up	4 weeks[cd]	

		PEARL I	PEARL II
OUTCOMES	**Primary end point**	Co-primary end points: Percentage of patients with reduction of uterine bleeding, defined as PBAC score < 75 at end of week 13; change in total fibroid volume (screening to week 13)	Percentage of patients with reduction of uterine bleeding, defined as PBAC score < 75 at end of week 13
	Secondary end points	Change in: bleeding pattern by PBAC, Hgb, Hct, ferritin, percentage of patients in amenorrhea, and global pain score by SFMPQ from baseline to week 5, 9, and 13; change in uterine volume from screening to week 13	
		Percentage of patients with Hgb > 12 g/dL and Hct > 36% at week 5, 9 and 13; reduction of ≥ 25% of total myoma volume at week 13; reduction of ≥ 25% of uterine volume at week 13; change from baseline to week 13 in the Measurement of Discomfort Due to UFs Questionnaire score	Change from screening to week 13 in total volume of three largest myomas; change from baseline to week 13 in UFS-QoL score
	Exploratory end points[d]	Change from baseline in: recorded bleeding pattern (PBAC) without hysterectomy or ablative intervention and global pain score (SFMPQ to weeks 26 and 38; and hemoglobin, hematocrit, and ferritin to weeks 17, 26, and 38; amenorrhea status at weeks 26 and 38 without hysterectomy or ablative intervention; proportion of patients whose surgery was cancelled due to symptomatic improvement and proportion of patients who underwent a less invasive procedure than originally planned; proportion of patients who received a blood transfusion, the number of transfusions per patient, and the transfusion volume used per patient.	
		Change in uterine and total myoma volumes from screening to weeks 26 and 38 without hysterectomy or myomectomy, and the change in uterine myoma-related symptoms from baseline to weeks 26 and 38.	Change in total volume of the three largest myomas from screening to weeks 17, 26, and 38 without hysterectomy or myomectomy; change in uterine volume from screening to weeks 17, 26, and 38 without hysterectomy; and the change in UFS-QoL score from baseline to weeks 26 and 38.
NOTES	**Publications**	Donnez et al. 2012[17]	Donnez et al. 2012[18]

ASA = acetylsalicylic acid; BMI = body mass index; GnRH = gonadotropin-releasing hormone; Hct = hematocrit; Hgb = hemoglobin; i.m. = intramuscularly; MRI = magnetic resonance imaging; N = population; OC = oral contraceptive; PAP = Papanicolaou test; PBAC = pictorial bleeding assessment chart; RCT = randomized controlled trial; SFMPQ = Short-form McGill Pain Questionnaire; SPRM = selective progesterone receptor modulator; UA = ulipristal acetate; UAE = uterine artery embolization; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life; US = ultrasound; UF = uterine fibroids.
Note: 1 additional report was included.[14]
[a]Screening to randomization (baseline) period.
[b]Randomized, double-blind treatment period (baseline to week 13 visit).
[c]End-of-treatment follow-up period.
[d]Both studies had two parts: active treatment (baseline to week 13 plus 4 weeks additional follow-up) and a non-treatment period (starting week 17 with all patients seen at weeks 26 and 38).
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

3.2 Included Studies

3.2.1 Description of Studies

PEARL I[10] and II[11] were both multinational, double-blind RCTs. The pre-randomization screening (run-in) period in both studies was five to eight weeks long. During this time period, an individual completed screening assessments to establish her eligibility to be enrolled in the studies (i.e., confirmed inclusion and exclusion criteria, completed medical history, physical and gynecological examination, uterine ultrasound, Papanicolaou [PAP] test, other lab tests, and endometrial biopsy if not performed in preceding six months), discontinued medications as per exclusion criteria, and used the pictorial bleeding assessment chart (PBAC) to assess extra-menstrual bleeding episodes. This time was also used to align patients` menstrual cycles with the start of the study treatment period and to confirm a surgery indication (i.e., hysterectomy, myomectomy, uterine artery embolization, or endometrium ablation).

Patients who successfully completed all screening assessments, met study inclusion criteria, and were at their first or second day of menstruation were randomized to treatment (baseline, treatment week 1) and followed for 13 weeks. At the end of 13 weeks (i.e., end of efficacy and safety assessments for the double-blind treatment period), treatment was stopped and patients still eligible for surgery underwent a surgical intervention as determined by the investigator; it should be noted that a less invasive procedure could have been performed than was originally planned or surgery could have been cancelled altogether. A post-treatment follow-up visit occurred for all patients, regardless of whether or not they had undergone surgery, at week 17. Patients could then enter the next study phase, during which no treatment was received and patients were assessed at weeks 26 and 38.

Each trial stratified randomization according to race (black or other); PEARL I additionally stratified patients according to hematocrit levels (≤ 28% or > 28%). Neither trial included clinical centres from North America. While PEARL I[10] was a placebo-controlled, superiority trial, PEARL II[11] was an active-controlled, non-inferiority trial of double-dummy design, which used a GnRH agonist (leuprolide 3.75 mg intramuscularly monthly) as the active comparator.

In PEARL I,[10] the co-primary end points were the percentage of patients with a PBAC score < 75 at 13 weeks, and the change in total fibroid volume from screening to week 13. In PEARL II,[11] the primary end point was the percentage of patients with a reduction of uterine bleeding (i.e., PBAC score < 75) at the end of week 13.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

PEARL I[10] and II[11] were similar with respect to their inclusion criteria, enrolling premenopausal women between the ages of 18 and 50 years with excessive menstrual blood loss secondary to the presence of UFs, who were candidates for surgical intervention. PEARL I[10] additionally specified a hemoglobin level of 10.2 g/dL or less for defining myoma-related anemia and that any anemia be non-macrocytic in nature.

Exclusion criteria between the two trials were also comparable. Neither trial permitted the enrolment of patients with most types of previous uterine surgery, endometrial ablation or uterine artery embolization, or with past or current endometrial hyperplasia or coagulopathy. In addition, PEARL II[11] did not enrol patients with past or current osteoporosis.

b) Baseline Characteristics

Baseline characteristics were generally well balanced between groups within the trials; however, a slight imbalance was noted in the mean PBAC score in both PEARL I (ulipristal > placebo) and PEARL II (leuprolide > ulipristal). Patients enrolled in PEARL I and II were predominantly white (~86%) with a mean age of 41 years and body mass index of 25 kg/m^2. Most (~94%) were of child-bearing potential. Patients in PEARL I were anemic with mean hemoglobin (Hgb) of 94 g/L, in contrast to PEARL II, whose patients were not anemic with mean Hgb of 122 g/L. However, mean ferritin levels were at the low end of normal for both PEARL I (12.7 mcg/L) and PEARL II (24.1 mcg/L) patients. Mean uterine volume at screening was greater in PEARL I (395 cm^3) than PEARL II patients (238 cm^3). Mean total myoma volume at screening was 140 cm^3 in PEARL I patients and was not available in PEARL II patients. The location of myoma varied across trials, with some imbalances noted between groups; the type of myoma recorded also varied across trials, but intramural myoma appeared to be the most commonly presenting type in each trial. At baseline, menstrual blood loss, as assessed by mean PBAC score, was greater in PEARL I (478 points) than PEARL II patients (389 points). Prior to study initiation, iron preparations were taken by about 6% of patients in PEARL I; in PEARL II, fewer patients assigned to ulipristal (2%) than leuprolide (6%) were taking an iron preparation prior to starting the study. The prior use of "antiinflammatory/antirheumatic products, non-steroids" was low in both trials and did not differ between groups within the trials. Likewise, the use of tranexamic acid and hormonal therapies was also low in each trial and similar between groups within the trials. Relevant surgical history was also unremarkable in the trials (Table 6).

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS (ITT)

Characteristic	PEARL I		PEARL II	
	UA 5 mg N = 95	PB N = 48	UA 5 mg N = 98	LA 3.75 mg N = 99
Age				
Mean (SD)	41.2 (5.9)	41.6 (5.6)	40.2 (6.2)	40.2 (6.2)
Race, n (%)				
Caucasian	84 (88.4)	41 (85.4)	84 (85.7)	83 (83.8)
Black	0	0	9 (9.2)	9 (9.1)
Asian	11 (11.6)	7 (14.6)	1 (1.0)	0
Hispanic	0	0	3 (3.1)	5 (5.1)
Other	0	0	1 (1.0)	2 (2.0)
Fertility status, n (%)				
Not of child-bearing potential	8 (8.4)	5 (10.4)	4 (4.1)	3 (3.0)
Of child-bearing potential	87 (91.6)	43 (89.6)	94 (95.9)	96 (97.0)
Body mass index (kg/m^2)				
Mean (SD)	25.9 (4.6)	24.6 (4.4)	25.4 (4.1)	24.9 (4.1)
Hemoglobin (g/dL)				
Mean (SD)	9.3 (1.5)[a]	9.6 (1.2)[a]	12.4 (1.6)[b]	12.1 (1.8)[b]
Hematocrit[a] (%)				
Mean (SD)	32.1 (4.1)[a]	32.5 (3.1)[a]	38.7 (4.0)[b]	38.3 (4.5)[b]

Characteristic	PEARL I		PEARL II	
	UA 5 mg N = 95	PB N = 48	UA 5 mg N = 98	LA 3.75 mg N = 99
Ferritin[a] (mcg/L)				
Mean (SD)	12.9 (20.1)[a]	12.4 (19.3)[a]	23.3 (23.1)[b]	24.8 (26.7)[b]
Uterine volume at screening (cm^3)				
Mean (SD)	392.1 (195.1)	401.6 (284.2)	240.2 (152.7)	236.5 (154.5)
Log_{10} mean (SD)	2.5 (0.2)	2.5 (0.3)	2.3 (0.3)	2.3 (0.3)
Total myoma volume at screening (cm^3)				
Mean (SD)	142.5 (133.3)	136.0 (191.4)	NR	NR
Log_{10} Mean (SD)	1.9 (0.6)	1.8 (0.7)	NR	NR
Total volume of three largest myomas at screening (cm^3)				
Mean (SD)	NR	NR	123.5 (137.1)	98.6 (98.3)
Log_{10} mean (SD)	NR	NR	1.9 (0.5)	1.8 (0.4)
Location of myoma,[c] n (%)[12]				
Anterior	121 (43)	39 (31)	72 (41)	60 (33)
Lateral	52 (19)	39 (31)	31 (18)	29 (16)
Lateral; anterior	0	0	3 (2)	5 (3)
Lateral; posterior	0	0	4 (2)	2 (1)
Posterior	107 (38)	50 (39)	66 (38)	87 (48)
Type of myoma,[c] n (%)[12]				
Submucosal	47 (17)	22 (17)	16 (9)	12 (7)
Submucosal, intramural	0	0	10 (6)	6 (3)
Submucosal, intramural, subserosal	0	0	2 (1)	4 (2)
Intramural	157 (56)	82 (64)	96 (55)	116 (63)
Intramural, subserosal	0	0	14 (8)	10 (6)
Subserosal	40 (14)	11 (9)	34 (19)	35 (19)
Pedunculated	0	0	3 (2)	0
Peduncular submucosal	26 (9)	9 (7)	1 (1)	0
Peduncular subserosal	10 (4)	4 (3)	0	0
PBAC				
Mean (SD)	487.4 (319.9)	459.8 (292.8)	374.0 (297.3)	402.9 (339.8)
SFMPQ, mean (SD)				
A	9.6 (9.0)	10.8 (9.0)	11.7 (9.6)	10.8 (9.7)
B - VAS	42.3 (29.2)	46.7 (28.9)	43.9 (24.5)	42.8 (25.9)
C - PPI	1.2 (1.1)	1.5 (1.3)	1.6 (1.3)	1.4 (1.2)
Measurement of Discomfort Due to Uterine Fibroids Questionnaire				
Mean (SD)	14.1 (5.2)	15.5 (4.0)	NR	NR
UFS-QoL, mean (SD)			N=56	N=50

Characteristic	PEARL I		PEARL II	
	UA 5 mg N = 95	PB N = 48	UA 5 mg N = 98	LA 3.75 mg N = 99
Symptom severity	NR	NR	53.1 (19.7)	53.7 (21.3)
HRQoL total score	NR	NR	54.2 (19.9)	49.4 (24.5)
Relevant prior medications[d]				
Iron preparations	6 (6.3)	3 (6.3)	2 (2.1)	6 (5.9)
Relevant surgical history[d]				
Caesarean section	6 (6.3)	4 (8.3)	8 (8.2)	4 (4.0)
Female sterilization	6 (6.3)	3 (6.3)	4 (4.1)	3 (3.0)
Salpingectomy	5 (5.3)	3 (6.3)	NA	NA
Uterine dilation and curettage	5 (5.3)	2 (4.2)	6 (6.2)	1 (1.0)
Cervical conisation	0	2 (4.2)	1 (1.0)	0
Cervical diathermy	1 (1.1)	2 (4.2)	0	1 (1.0)
Cervix cautery	1 (1.1)	0	NA	NA
Oophorectomy	1 (1.1)	0	1 (1.0)	0
Ovarian cystectomy	1 (1.1)	1 (2.1)	1 (1.0)	1 (1.0)
Salpingo-oophorectomy unilateral	1 (1.1)	0	NA	NA
Fallopian tube operation	0	1 (2.1)	NA	NA
Salpingo-oophorectomy	1 (1.1)	0	NA	NA
Uterine polypectomy	1 (1.1)	0	NA	NA
Uterine operation	NA	NA	0	1 (1.0)

HRQoL = health-related quality of life; ITT = intention-to-treat; LA = leuprolide acetate; n = subpopulation; N = population; NA = not applicable; NR = not reported; PB = placebo; PBAC = pictorial bleeding assessment chart; PPI = present pain intensity; SD = standard deviation; SFMPQ = Short-Form McGill Pain Questionnaire; UA = ulipristal acetate; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire; VAS = visual analogue scale.
[a]Values irrespective of transfusions.
[b]Values prior to transfusion only.
[c]Evaluation performed by MRI in PEARL I and by transvaginal ultrasound in PEARL II.[12]
[d]Safety population.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

c) Interventions

Patients were randomized in PEARL I[10] (2:2:1) and PEARL II[11] (1:1:1) to one of three treatment groups: ulipristal 5 or 10 mg orally once daily or comparator — either placebo (PEARL I) or leuprolide 3.75 mg intramuscularly monthly (PEARL II). Because the 10 mg dose is not a Health Canada–approved dose, only data for the 5 mg dose are presented. In PEARL I[10] only, all patients received co-treatment of an oral iron supplement (ferrous sulphate 256.3 mg containing 80 mg elemental iron) taken once daily; dosing was adjusted at the investigator's discretion. In PEARL II,[11] blinding was achieved through a double-dummy design employing matching placebos for both study treatments. The use of progestins, oral

contraceptives, acetylsalicylic acid, mefenamic acid, anticoagulants, antifibrinolytics, or systemic glucocorticoids was not permitted during either trial.[10,11]

d) Outcomes

Efficacy

The co-primary efficacy outcomes in PEARL I were the percentage of patients with a PBAC score < 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 < 75 at the end of 13 weeks.

Secondary efficacy outcomes common to both trials were the change in bleeding pattern by PBAC score, hemoglobin, hematocrit, ferritin, percentage of patients in amenorrhea (i.e., PBAC $\leq$ 2), and global pain score by Short-form McGill Pain Questionnaire (SFMPQ) from baseline to week 5, 9, and 13; change in uterine volume from screening to week 13. Of note, myoma volume evaluation was by magnetic resonance imaging (MRI) in PEARL I and transvaginal ultrasound in PEARL II; only MRI data were subject to centralized reading.

In PEARL I, additional secondary efficacy outcomes comprised the percentage of patients with hemoglobin > 12 g/dL and hematocrit > 36% at week 5, 9 and 13; reduction of ≥ 25% in total myoma volume at week 13; reduction of ≥ 25% in uterine volume at week 13, and change from baseline to week 13 in the Measurement of Discomfort Due to Uterine Fibroids Questionnaire score. In PEARL II, the change in total volume of the three largest myomas from screening to week 13 and the change from baseline to week 13 in Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QoL) score were additional secondary efficacy outcomes.

Exploratory efficacy outcomes common to both trials were the change from baseline in recorded bleeding pattern (PBAC) without hysterectomy or ablative intervention and global pain score (SFMPQ) to weeks 26 and 38; hemoglobin, hematocrit, and ferritin to weeks 17, 26, and 38; amenorrhea status at weeks 26 and 38 without hysterectomy or ablative intervention; proportion of patients whose surgery was cancelled due to symptomatic improvement and proportion of patients who underwent a less invasive procedure than originally planned; proportion of patients who received a blood transfusion, the number of transfusions per patient, and the transfusion volume used per patient.

In PEARL I, additional exploratory efficacy outcomes comprised the change in uterine and total myoma volumes from screening to weeks 26 and 38 without hysterectomy or myomectomy, and the change in uterine myoma-related symptoms from baseline to weeks 26 and 38. In PEARL II, additional exploratory efficacy outcomes included the change in total volume of the three largest myomas from screening to weeks 17, 26, and 38 without hysterectomy or myomectomy; change in uterine volume from screening to weeks 17, 26, and 38 without hysterectomy; and the change in UFS-QoL score from baseline to weeks 26 and 38.

Four patient self-report instruments were administered during the course of the trials to assess menstrual blood loss (PBAC — both trials), pain (SFMPQ — both trials), fibroid-related symptoms and health-related quality of life (UFS-QoL Questionnaire — PEARL II only), and fibroid-related discomfort (Measurement of Discomfort Due to Uterine Fibroids Questionnaire — PEARL I only). All of the instruments except the Measurement of Discomfort Due to Uterine Fibroids have been previously validated, but none have published minimal clinically importance differences (MCIDs) (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).

Harms

Safety data (SAEs, AEs, and WDAEs) were presented through week 17 for both studies. In PEARL II, the manufacturer additionally pre-specified two primary safety outcomes to test for the superiority of ulipristal compared with leuprolide using the safety analysis set: mean serum estradiol (E2) levels at week 13 and the percentage of patients who experienced moderate or severe hot flashes during the treatment period; no definition for "moderate or severe" was provided. It should be noted that consultation with the clinical expert for this review revealed that measuring hormone levels is not part of the standard of care in the management of UFs and, consequently, was not identified as a relevant outcome in the systematic review protocol.

3.2.3 Statistical Analysis

e) Efficacy Criteria

Primary Efficacy Outcomes

In PEARL I, the superiority of ulipristal compared with placebo was tested on the co-primary efficacy outcomes (i.e., reduction in uterine bleeding as determined by the percentage of patients with PBAC score < 75 at 13 weeks and the change in total fibroid volume as determined by MRI from screening to week 13). For PBAC scores, data were presented descriptively, with between-group comparisons conducted using Cochran–Mantel–Haenszel (CMH) testing at the two-sided significance level of $P = 0.05$ while controlling for strata (i.e., hematocrit, race). Confidence intervals (CIs) for the between-group treatment difference were calculated using the Newcombe–Wilson score method (uncorrected).[10] Total myoma volumes were reported descriptively for both the raw and log-transformed data. Between-group comparisons on the changes were conducted using analysis of covariance. With the change in total myoma volume from screening to week 13 serving as the dependent variable, treatment assignment, log total myoma volume at screening, and strata were additional terms incorporated into the model; estimated mean treatment group differences compared with placebo, *P* values, and CIs were subsequently calculated. As assumptions of the parametric analysis were deemed invalid (non-normally distributed data), data were log-transformed and analyzed parametrically. As well, the percentage change in total myoma volume from screening to week 13 was analyzed non-parametrically (Hodges-Lehmann point estimator and Moses confidence interval). Hence, the nonparametric analysis of total myoma volume was reported as the primary analysis with the parametric as supportive analysis.[10]

For continuous outcomes, missing data for outcomes analyzed via repeated measures analysis of variance methods were not imputed separately as they were adjusted for in the analysis itself, while the last observation carried forward (LOCF) method was used for all other outcomes with available post-baseline data. A value remained missing if there was no post-baseline non-missing value, and in which case the patient was excluded from the analysis for the outcome.[10]

The sample size calculation for PEARL I was based on demonstrating superiority of ulipristal versus placebo for analysis of total myoma volume. This efficacy outcome was used because — according to the investigators — total myoma volume required more participants than the analysis of percentage of patients with PBAC < 75 at week 13 in order to achieve ≥ 90% power for each primary efficacy outcomes, using two sided tests with type I error rates of 5% and a Bonferroni correction for the two dose comparisons.[10] Analysis of change in total myoma volume was conducted after taking logarithms of the data. The investigators assumed an average difference in the change in log total myoma volume from screening to week 13 between ulipristal and placebo of –0.1 (20% change from screening), and a between patient standard deviation of 0.15. They estimated a 10% on-treatment drop-out rate, meaning 240 patients were required to be randomized to ensure adequate power (96 patients per ulipristal group and 48 in placebo).[10]

In PEARL II, the non-inferiority of ulipristal compared with leuprolide was tested on the primary efficacy outcome (i.e., percentage of patients with a reduction in uterine bleeding as defined by a PBAC score < 75 at week 13) using a one-sided CI at a significance level of $P = 0.025$ against a –20% non-inferiority margin — a clinical margin deemed acceptable by the clinical expert consulted by CDR for this review — while controlling for strata (i.e., race). CIs for the between-group treatment difference were calculated using the Newcombe–Wilson score method (uncorrected). Missing data were imputed using the LOCF. Analyses of non-inferiority were conducted using the per-protocol (PP) analysis set with supportive analyses performed using the intention-to-treat (ITT) analysis set.[11]

The sample size calculation for PEARL II was based on demonstrating non-inferiority of ulipristal versus leuprolide with ≥ 90% power and to ensure sufficient patient exposure for an overall safety assessment; this resulted in 300 patients required to be randomized (100 per treatment group). A Bonferroni correction was applied to the alpha for the two dose ulipristal comparisons, with a pre-specified non-inferiority margin of 20%. The calculation assumed that the ulipristal and leuprolide response rates would both be 85%, and a 15% on-treatment drop-out rate and protocol violators.[11]

In both studies, comparisons were tested separately for the two ulipristal doses (5 mg and 10 mg), so a Bonferroni correction was used to adjust for multiplicity. No adjustment was used to account for the fact that there are two primary efficacy outcomes in PEARL I because a successful outcome was only deemed to occur if at least one of the 5 mg or 10 mg ulipristal treatments resulted in a statistically significant improvement versus placebo with regards to both outcomes.[10]

Secondary Efficacy Outcomes

In PEARL I, all secondary efficacy outcomes were summarized descriptively by treatment assignment and time point (weeks 5, 9, and/or 13). Changes from baseline in bleeding patterns from PBAC scoring were analyzed using non-parametric testing controlling for strata; between-group comparisons in the percentage of patients in amenorrhea (PBAC $\leq$ 2) were conducted using CMH testing and the Newcombe–Wilson score method (uncorrected) for calculating CIs for the between-group treatment difference. Changes in hematologic indices were analyzed using repeated measures analysis of covariance covarying for baseline levels; additional analyses on pre-transfusion data were conducted in the event of patients requiring transfusions. Between-group comparisons of the percentage of patients with hemoglobin > 12 g/L and hematocrit > 36% at each time point were conducted using CMH testing and the Newcombe-Wilson score method (uncorrected) for the between-group treatment difference CI. Changes in uterine volume were analyzed using analysis of covariance covarying for uterine volume at screening. The SFMPQ was analyzed using non-parametric testing on the absolute change from baseline; data imputation (i.e., using the mean of the two available measurements) may have occurred in cases of missing data. The Measurement of Discomfort Due to Uterine Fibroids Questionnaire — a functional derivative of the UFS-QoL created in-house by the manufacturer to manage around the non-availability of a disease-specific QoL instrument meeting all the linguistic needs of the trial — analyzed and handled data in a similar way to the SFMPQ.[10]

In PEARL II, all secondary efficacy outcomes were summarized descriptively by treatment assignment and time point. Changes from baseline in bleeding patterns from PBAC scoring were analyzed using non-parametric testing; between-group comparisons in the percentage of patients in amenorrhea (PBAC $\leq$ 2) were conducted as in PEARL I. In addition, Kaplan–Meier curves were used to describe the time to no bleeding for each treatment group. Changes in hematologic indices were analyzed as in PEARL I (repeated measures analysis of covariance). The change in uterine volume and total volume of the three largest myomas was analyzed using analysis of covariance covarying for screening volume; data

imputation (i.e., using the mean of the two available measurements) may have occurred in cases of single missing dimensions. The SFMPQ was analyzed as in PEARL I. The UFS-QoL was analyzed using analysis of covariance on the absolute change from baseline covarying for the baseline score; data were not collected from Poland, as the UFS-QoL was not available in the Polish language. The handling of missing data for the UFS-QoL was not described.[11]

Analyses of secondary outcomes were adjusted for multiple comparisons using a Bonferroni correction, but only because comparisons were tested separately for the two ulipristal doses (5 mg and 10 mg). No adjustment was made for significance testing of multiple secondary outcomes.

Tertiary Efficacy Outcomes

Although these were exploratory outcomes in PEARL I and II, planned and completed surgeries were summarized descriptively while statistical testing using the Newcombe–Wilson score method (uncorrected) with 95% CI estimation was used to compare differences between groups in the percentage of patients who were switched to less invasive surgery.

Harms Criteria

In PEARL II, but not PEARL I, two co-primary safety end points were additionally pre-specified (mean serum estradiol levels at week 13 and the percentage of patients who experienced moderate or severe hot flashes throughout the treatment period) in order to test for the superiority of ulipristal compared with leuprolide on safety. Using the safety analysis set as the primary analysis and the PP analysis set as a supportive analysis, between-group comparisons were conducted using a two-sided CI at the $P = 0.05$ significance level. CMH testing was used to compare the between-group difference in the proportion of patients reporting moderate or severe hot flashes as AEs during the treatment period, adjusted for race; the Newcombe-Wilson score method (uncorrected) was used to calculate the associated CI around the difference.[11] It should be noted that consultation with the clinical expert for this review revealed that measuring hormone levels is not part of the standard of care in the management of UFs and, consequently, was not identified as a relevant outcome in the systematic review protocol.

f) Analysis Populations

The primary analysis set for performing efficacy analyses in PEARL I was the ITT analysis set, while in PEARL II it was the PP analysis set; the ITT was a secondary analysis set used in PEARL II for supporting the findings from the PP analysis set. For both trials, the ITT analysis set included all randomized patients who received at least one dose of study drug and had post-baseline data for at least one efficacy outcome. The PP analysis set included all randomized patients who received at least one dose of study drug, had post-baseline data for at least one efficacy outcome, and had not committed any major protocol violations. The safety analysis set included all randomized patients who received at least one dose of study drug (Table 7).

3.3 Patient Disposition

In PEARL I,[10] a total of 242 patients were randomized, 144 of them to ulipristal 5 mg (n = 96) or placebo (n = 48). Only one patient randomized to ulipristal 5 mg never received treatment. The ITT set comprised 237 (97.9%) patients, of whom 224 (92.6%) completed 13 weeks of treatment, including 89 (92.7%) randomized to ulipristal 5 mg and 45 (93.8%) randomized to placebo. Reasons for premature discontinuation varied without obvious pattern and are described in Table 7.

In PEARL II,[11] a total of 307 patients were randomized, 204 of them to ulipristal 5 mg (n = 102) or leuprolide (n = 102). Two patients — one from the 5 mg arm and one from the 10 mg arm — never received treatment. The ITT set comprised 298 (97.1%) patients, of whom 292 (95.1%) completed 13 weeks of treatment, including 97 (95.1%) randomized to ulipristal 5 mg and 96 (94.1%) randomized to leuprolide. Reasons for premature discontinuation varied, but were mainly due to AEs (4.9%) in the case of patients taking leuprolide (Table 7).

TABLE 7: PATIENT DISPOSITION

	PEARL I		PEARL II	
	UA 5 mg	**PB**	**UA 5 mg**	**LA 3.75 mg**
Screened, N	462		400	
Randomized, N (%)	96 (39.7)	48 (19.8)	102 (33.2)	102 (33.2)
Discontinued, N (%)	7 (7.3)	3 (6.3)	5 (4.9)	6 (5.9)
Discontinuation reason:				
Lack of efficacy	2 (2.1)	0	0	0
Adverse event (unrelated)	0	0	1 (1.0)	5 (5.0)
Patient request	1 (1.0)	2 (4.2)	2 (2.0)	1 (1.0)
Protocol deviation	2 (2.1)	0	0	0
Lost to follow-up	2 (2.1)	1 (2.1)	1 (1.0)	0
ITT, N	95	48	98	99
PP, N	85	45	93	93
Safety, N	95	48	97	101

ITT = intention-to-treat; LA = leuprolide acetate; N = population; PB = placebo; PP = per-protocol; UA = ulipristal acetate.
Note: The 10 mg group was not presented as it is not an approved dose.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

3.4 Exposure to Study Treatments

In PEARL I, the mean (standard deviation [SD]) exposure to study treatment was 87.2 (11.3) days in ulipristal-treated patients and 89.0 (6.1) days in placebo-treated patients.[10]

In PEARL II, the mean (SD) exposure to ulipristal or placebo was 88.8 (8.1) days in ulipristal-treated patients and 86.8 (11.3) days in placebo-treated patients. Exposure to leuprolide or saline was based on adherence to the three study visits when the injection was administered; accordingly, 95 (97.9%) patients in the ulipristal group and 98 (97.0%) patients in the leuprolide group reportedly received all three injections.[11]

3.5 Critical Appraisal

3.5.1 Internal Validity

Both PEARL I and II were double-blind, randomized, controlled (placebo-PEARL I, active comparator-PEARL II), parallel-group trials; PEARL II was also double-dummy in design. Appropriate randomization methods and allocation concealment (i.e., via an interactive voice or web response system) were used. Both trials stratified by race (black or other) and PEARL I additionally stratified by screening hematocrit level (≤ 28% or > 28%); there was no stratification by study centre. Dosing of leuprolide was considered appropriate in PEARL II according to the clinical expert involved in the review.

Blinding in PEARL II may have been compromised by the incidence of AEs — particularly, hot flashes — in the leuprolide group; this is of importance, given the subjective nature of the primary outcome of the trial.

Baseline characteristics were mostly similar across treatment groups in both trials, except for baseline mean PBAC scores, where slightly higher scores were observed in the ulipristal group in PEARL I and in the leuprolide group in PEARL II. During PEARL II, more patients assigned to ulipristal (32.0%) took an iron supplement concomitantly than those assigned to leuprolide (24.8%); this could have advantaged ulipristal treatment on hematological outcomes. Concomitant antiinflammatory, antirheumatic, or NSAID medication use was similar between ulipristal and comparator groups, respectively, within PEARL I (12.6% versus 8.3%) and II (28.9% versus 27.7%), although higher overall use was noted in PEARL II.

The pre-specified non-inferiority margin in PEARL II was 20%. According to the manufacturer, it was chosen based on clinical considerations: "the 20% margin is rather small in comparison with the expected difference in efficacy of each treatment versus no treatment or versus placebo"; and "an oral treatment that is well tolerated could easily be 20% less effective in inducing amenorrhea or in reducing menstrual blood loss than the GnRH agonist leuprorelin, but still be regarded as equivalent or even superior to leuprorelin in terms of clinical utility and benefit/risk."[11] The non-inferiority margin was deemed appropriate by the clinical expert consulted by CDR. The 20% margin is considerably smaller than the difference observed between ulipristal and placebo in PEARL I. However, the non-inferiority margin could otherwise not be evaluated against data from other trials of GnRH agonists using the PBAC, as no such published trials were identified.

In the non-inferiority PEARL II trial, the primary efficacy outcome was appropriately analyzed using both the PP and ITT analysis sets. The number of premature withdrawals was low in both trials and similar between groups, with more than 92% of participants completing 13 weeks of follow-up; however, this completion rate was based on the ITT analysis set, which was defined (in both studies) as "…all randomized subjects who used the trial medication at least once, and who had post-baseline, that is, on-treatment, efficacy data for at least one efficacy end point."[10,11] This definition is more in line with a modified ITT population rather than one that comprises all randomized patients. Nonetheless, the small numerical difference in the number of patients randomized and analyzed as the ITT population in both studies is unlikely to have an important impact on outcomes.

Various patient self-report instruments were used in the trials. The PBAC was used to evaluate the primary outcome in both PEARL I and II and, although an accepted instrument for use in clinical trials, it is not regularly used in clinical practice. Additionally, the PBAC becomes less well correlated with menstrual blood loss with higher volumes of blood loss.[8] Given that the women enrolled were determined to have levels of menorrhagia well above the PBAC threshold for menorrhagia (i.e., > 100) at baseline, it is unclear to what extent changes in PBAC scores, especially changes in higher scores, reflect changes in blood loss, let alone those occurring as a function of treatment. Nonetheless, control of bleeding (PBAC < 75) was achieved in $\geq$ 90% of ulipristal-treated patients in both trials at week 13. No information regarding the MCID with the PBAC has been published (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).

The SFMPQ, used in both trials, is a validated instrument used to assess pain generally; there were no published MCIDs found for the SFMPQ. The Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL), used in PEARL II, is also a validated instrument, but without published MCIDs; although an

MCID of five points has been suggested in one paper, this number appears based on clinician opinion and not the result of formal derivation.[19] The Measurement of Discomfort Due to Uterine Fibroids Questionnaire used in PEARL I was derived from the UFS-QoL; it was created in-house by the manufacturer to manage around the inability of the UFS-QoL (or other disease-specific QoL instrument) to meet all the linguistic needs of the trial.[10] It is not clear to what extent this derivative questionnaire was validated, particularly in the setting of multiple languages. Of note, the UFS-QoL was nonetheless used in PEARL II, but not in Polish patients, as a validated Polish version of the questionnaire did not exist; however, Polish patients comprised nearly half (~47%) of the trial's patients.[11]

The definition of anemia varied somewhat between PEARL I and II, where PEARL II further characterized anemia (i.e., hemoglobin $\leq$ 12 g/dL) as moderate to severe in nature (i.e., hemoglobin $\leq$ 10.2 g/dL), whereas PEARL I simply referred to anemia as hemoglobin $\leq$ 10.2 g/dL. Such nuance may be of relevance when interpreting and comparing post-treatment hematological status between trials.

Analyses in both trials were adjusted for multiplicity due to more than one ulipristal treatment group (two groups: 5 mg and 10 mg) using a Bonferroni correction. However, no adjustment was made for testing multiple secondary outcomes, which could inflate the type I error rate of these analyses.

3.5.2 External Validity

Both PEARL I and II were conducted outside of North America, so it is possible Canadian clinicians may have recommended different surgical interventions in the same patients, due to differences in clinical practice, clinical training, or resource availability. There were few black patients — a disproportionately affected group — studied in either trial, a limitation for generalizing to North American practice, but likely a less relevant racial group among the participating countries.

Although GnRH agonists, such as leuprolide, were identified as a key comparator in PEARL II, other hormonal therapies employed in clinical practice for management of UFs include combined hormonal contraceptives, progestins, and progestin intrauterine system; no trials with these comparators were identified. The treatment regimen for leuprolide (i.e., 3.75 mg administered intramuscularly every month for three months) in PEARL II was considered appropriate. The duration of the trials (i.e., 13 weeks) was likely appropriate for assessing treatment efficacy. (Of note, the ulipristal product monograph states that the safety of ulipristal — particularly with respect to the potential risk of drug class–related adverse effects on the endometrium — with use for a period longer than three months or on repeat courses of treatment is unknown; hence, treatment duration is limited to three months.[14])

The trials were not designed to assess differences in surgical outcomes as a function of treatment; an important limitation, especially given that most of the literature in this therapeutic area appears to focus on the effect of treatment on surgical outcomes, such as intra- or post-operative complication rates. Furthermore, in PEARL I and II medical treatment was administered for a defined three-month period as an antecedent to surgery; hence, it is unclear how relevant the assessment of quality of life is during this relatively short pre-surgical period compared with the post-operative period. Because surgical interventions in both PEARL I and II trials occurred after the 13-week randomization period, and at the discretion of each clinical site investigator, it is difficult to draw any conclusions about potential differential effects that may have arisen as a result of medical pre-treatment. Nonetheless, it is interesting to note the low number of patients who actually completed surgery in both trials; no explanation was provided as to why the surgeries did not take place.

Two co-primary safety end points were pre-specified in PEARL II, which included the serial measurement of serum estradiol levels. Consultation with the clinical expert for this systematic review, however, indicated that measuring hormone levels is not part of the standard of care in the management of UFs.

Leuprolide was administered without hormonal therapy add-back in PEARL II. GnRH agonists administered alone induce symptoms similar to menopause, including but not limited to hot flashes, sleep disorders, emotional symptoms, and bone loss. Add-back hormonal therapy is recommended in the Society of Obstetricians and Gynaecologists of Canada guidelines when GnRH agonists are used for the treatment of endometriosis[9] in order to minimize such symptoms without affecting pain outcomes. However, based on discussion with the clinical expert involved in the review, hormone add-back therapy is not universally done in the setting of UFs; some clinicians may opt to treat with a GnRH agonist alone for a period not exceeding six months, as add-back therapy also carries with it the risk of incompletely suppressing the growth or proliferation of UFs.[4] Because the use of GnRH agonist therapy used in PEARL II was unopposed, the incidence of AEs in the leuprolide group is expected to be higher than would be observed in clinical practice, potentially favouring ulipristal. The impact of AEs is also expected to reflect negatively on the quality of life measures, once again favouring ulipristal. Nevertheless, no meaningful differences between treatment groups across quality of life scales were reported in PEARL II.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (see Section 2.2, Table 4). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data. Although the systematic review protocol identified the subpopulation of black patients as a subgroup analysis of interest and both trials did stratify by race (i.e., black or other), there were too few black patients (none in PEARL I and < 10% in PEARL II) for subgroup analyses.

3.6.1 Quality of Life

a) Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire

PEARL I

This questionnaire was not employed in PEARL I.

PEARL II

There were no statistically significant differences between groups in either the symptom severity score (difference: –1.0; 95% CI, –10.4 to 8.4) or HRQoL total score (difference: 2.5; 95% CI, –7.3 to 12.3) from baseline to week 13 (Appendix 4, Table 10).

3.6.2 Symptom Control

b) Measurement of Discomfort Due to Uterine Fibroids Questionnaire

PEARL I

A statistically significant difference in the median change from baseline to week 13 in discomfort due to UFs favouring ulipristal over placebo was shown (difference: –4.0; 95% CI, –6.0 to –1.0) (Appendix 4, Table 12). There is no published information on MCID or on the validity of this questionnaire, however, making the interpretation of these findings uncertain.

PEARL II

This questionnaire was not employed in PEARL II.

c) Short-form McGill Pain Questionnaire

PEARL I

There were no statistically significant differences between groups from baseline to week 13 in any of the three components of the questionnaire (Appendix 4, Table 11).

PEARL II

There were no statistically significant differences between groups from baseline to week 13 in any of the three components of the questionnaire (Appendix 4, Table 11).

3.6.3 Other Efficacy Outcomes

a) Number (%) of Patients Not Proceeding to Surgery after Treatment

Proportion of patients for whom surgery was cancelled because of improvement of symptoms was an exploratory outcome in both PEARL I and II; consequently, no between-group comparisons were estimated. In PEARL I, 65.6% of ulipristal-treated patients compared with 72.9% of placebo-treated patients did not proceed to surgery.[10] In PEARL II, 55.9% of ulipristal-treated patients compared with 53.8% of leuprolide-treated patients did not proceed to surgery[11] (Appendix 4,Table 13).

b) Number (%) of Invasive Surgeries (i.e., Laparotomic Hysterectomy) Avoided

Proportion of patients switched to less invasive surgery was an exploratory outcome in both PEARL I and II. In PEARL I, 69.9% of ulipristal-treated patients compared with 77.1% of placebo-treated patients were switched to less invasive surgery.[10] In PEARL II, 62.0% of ulipristal-treated patients compared with 59.1% of leuprolide-treated patients were switched to less invasive surgery[11] (Appendix 4, Table 13). Types of surgeries planned and completed for both PEARL I and II are summarized in Table 14 (Appendix 4).

c) Control of Bleeding

The hematin alkaline test is considered the gold standard for quantifying menstrual blood loss,[8] but was not used in either trial due to practical considerations;[10,11] instead, a semi-quantitative instrument known as the PBAC was used. (Refer to APPENDIX 5: VALIDITY OF OUTCOME MEASURES for details.)
A reduction in excessive bleeding was defined as achieving a PBAC score < 75. The proportion of patients who achieved a PBAC score < 75 at the end of 13 weeks of treatment was the primary efficacy outcome for both PEARL I and II, and the basis for testing the non-inferiority of ulipristal compared with GnRH agonist therapy (leuprolide) in PEARL II.

PEARL I

A statistically significantly greater proportion of patients treated with ulipristal compared with placebo achieved a PBAC score < 75 at week 13 (difference: 72.7%; 95% CI, 55.1% to 83.2%). The findings were similar in a sensitivity analysis of the last 28 days under treatment, where a greater proportion of ulipristal-treated patients achieved a PBAC score < 75 compared with placebo-treated patients (difference: 67.5%; 95% CI, 49.4% to 79.2%) (Appendix 4, Table 15). Although no formal statistical testing was performed, a similar pattern was observed in the proportion of patients who achieved a PBAC score < 75 at week 9 (86% versus 15%), but not at week 5 (5% versus 2%).[12] The median change in PBAC score from baseline to week 13 was –328.5 and –59.0 in the ulipristal and placebo group, respectively (difference: –291.0; 95% CI, –399.0 to –194.0) (Appendix 4, Table 16). A higher proportion of patients treated with ulipristal (73.4%) compared with placebo (6.3%) were in amenorrhea (i.e., PBAC < 2) at week 13 (difference: 67.2%; 95% CI, 50.2% to 77.0%) (Appendix 4, Table 17).

PEARL II

There were no statistically significant differences between ulipristal and leuprolide groups in the primary (PP) analysis of the proportion of patients who achieved a PBAC score < 75 at week 13 (difference: 1.2%; 95% LCL, –9.3%); this finding was supported by the ITT analysis (difference: 1.0%; 95% LCL, –9.4%). The non-inferiority hypothesis was therefore confirmed based on the pre-specified non-inferiority margin of –20%. The findings were similar in a sensitivity analysis of the last 28 days under treatment, where there was no statistically significant difference between groups in the proportion of patients achieving a PBAC score < 75, whether by the PP analysis (difference: 3.3%; 95% LCL, –6.7%) or ITT analysis set (difference: 3.1%; 95% LCL, –6.9%) (Appendix 4, Table 15). Although no formal statistical testing was performed, a similar pattern was observed in the PP analysis set in the proportion of patients who achieved a PBAC score < 75 at week 9 (93% versus 88%), but not at week 5 (8% versus 4%); results were similar for the ITT set.[12] The median change in PBAC score from baseline to week 13 was –268.0 and –273.5 in the ulipristal and leuprolide groups, respectively (difference: 6.0; 95% CI, –54.0 to 63.0); results were similar using the ITT analysis set (Appendix 4, Table 16). A similar proportion of patients treated with ulipristal (75.3%) compared with leuprolide (80.4%) were in amenorrhea (i.e., PBAC < 2) at week 13 (difference: –5.2%; 95% CI, –18.7% to 8.6%) (Appendix 4, Table 17). The time to achievement of a PBAC score < 75 was examined in an exploratory manner without formal statistical testing. Ulipristal-treated patients achieved PBAC < 75 in a median of three days (95% CI, two days to four days) while leuprolide-treated patients took a median of six days (95% CI, four days to 11 days) using the PP analysis set; findings were similar for the ITT analysis set.[12] Similarly, in an exploratory analysis of the time to achievement of amenorrhea, ulipristal-treated patients took a median of eight days (95% CI, six days to 15 days) while leuprolide-treated patients took a median of 23 days (95% CI, 14 days to 28 days); findings were similar for the ITT analysis set.[12]

d) Reversal of Anemia, If Present

PEARL I

For entry into PEARL I, patients had to have myoma-related anemia (i.e., hemoglobin $\leq$ 10.2 g/dL); all patients, regardless of treatment assignment, were prescribed a daily iron supplement (80 mg elemental Fe^{2+}). After 13 weeks of treatment, statistically significant increases in both hemoglobin (adjusted LS mean difference: 0.9; 95% CI, 0.4 to 1.4) and hematocrit (difference: 2.6; 95% CI, 1.0 to 4.1) were noted, favouring ulipristal treatment over placebo in both cases. There was no difference observed between groups in ferritin levels (Appendix 4, Table 18). At the end of 13 weeks, hemoglobin values rose above 12 g/dL in a majority of patients: 85.3% and 77.1% of patients receiving ulipristal and placebo, respectively; moderate to severe anemia was present in 3.2% of ulipristal-treated patients and 8.3% of placebo-treated patients. The number of patients requiring blood transfusions during the trial was small overall, with 98.9% of ulipristal- and 100.0% of placebo-treated patients not requiring any transfusions.[10]

PEARL II

For entry into PEARL II, patients did not have to be anemic; iron supplementation, taken concomitantly by 32.0% of ulipristal-treated patients and 24.8% of leuprolide-treated patients, was not administered systematically as a co-treatment. After 13 weeks of treatment, the PP analysis revealed no statistically significant differences in hemoglobin (adjusted LS mean difference: –0.0; 95% CI, –0.3 to 0.3), hematocrit (difference: –0.0; 95% CI, –0.9 to 0.8), or ferritin levels between groups (difference: –0.6; 95% CI, –6.2 to 5.0); results were similar with the ITT analysis set (Appendix 4, Table 18). At baseline, 39.6% of ulipristal-treated patients and 41.1% of leuprolide-treated patients were considered anemic (i.e., Hgb $\leq$ 12 g/dL); of these, 11.0% and 18.9%, respectively, had moderate to severe anemia (i.e., Hgb $\leq$ 10.2 g/dL).

At the end of 13 weeks, hemoglobin values rose above 12 g/dL in 77.4% of ulipristal-treated and 76.3% of leuprolide-treated patients; moderate to severe anemia persisted in 5.4% and 8.6%, respectively. The number of patients requiring blood transfusions during the trial was small overall, with 98.0% of patients in each group not requiring any transfusions.[11]

e) Total Myoma Volume

PEARL I

A statistically significant reduction in total myoma volume — a co-primary efficacy outcome — was observed from screening to week 13 favouring ulipristal treatment (median difference: –22.6%; 95% CI, –36.1% to –8.2%); no statistically significant difference between ulipristal and placebo groups was observed, however, when the raw data were log-transformed (Appendix 4, Table 19). A higher proportion of ulipristal-treated patients achieved > 25% reduction in myoma volume at week 13 compared with placebo (difference: 23.4%; 95% CI, 4.1% to 38.7%) (Appendix 4, Table 21).

PEARL II

There were no data available for PEARL II on the change in total myoma volume. Instead, the change in the log-transformed volume of the three largest myomas was reported from screening to week 13, for which there was no statistically significant difference noted between ulipristal and leuprolide groups by PP analysis; however, the ITT analysis showed a statistically significantly greater reduction in patients treated with leuprolide than ulipristal (adjusted LS mean difference: 0.10; 95% CI, 0.01 to 0.19) (Appendix 4, Table 20).

f) Uterine Volume

PEARL I

A statistically significant reduction in the log-transformed uterine volume from screening to week 13 was observed in ulipristal-treated patients compared with placebo (adjusted LS mean difference: –0.08; 95% CI, –0.13 to –0.03) (Appendix 4, Table 22). A higher proportion of ulipristal-treated patients achieved $\geq$ 25% reduction in uterine volume at week 13 compared with placebo (difference: 27.7%; 95% CI, 11.3% to 40.4%) (Appendix 4, Table 21). No corresponding median percentage changes were reported.

PEARL II

A statistically significant reduction in the log-transformed uterine volume from screening to week 13 favouring leuprolide was observed by PP analysis (adjusted LS mean: 0.17; 95% CI, 0.10 to 0.24) (Appendix 4, Table 22). Results from the ITT analysis were similar, favouring leuprolide. The median percentage change in uterine volume observed from screening to week 13 was –20.4% and –47.1% in the ulipristal and leuprolide groups, respectively.[11]

3.7 Harms

3.7.1 AEs

AEs were more common overall in PEARL II than in PEARL I, where 80.8% and 48.3% of patients, respectively, experienced one or more AEs. In PEARL I, the frequency of AEs was similar between ulipristal (49.5%) and placebo (45.8%) groups, but appeared lower in ulipristal (77.3%) than leuprolide-treated (84.2%) patients in PEARL II. In PEARL I, the distribution of AEs was unremarkable, with the most common AEs occurring at a frequency of 4.2%; for ulipristal-treated patients, headache (4.2% versus 4.2%) and constipation (4.2% versus 2.1%) were the most common AEs compared with placebo. In PEARL II, hot flashes (25.8% versus 65.3%) and headache (25.8% versus 28.7%) were the most common AEs, with hot flashes occurring notably more frequently in leuprolide-treated patients. Abdominal pain

(3.1% versus 8.9%) and acne (0 versus 5.0%) were also more common in leuprolide-treated patients. No AEs among ulipristal-treated patients occurred at a frequency in excess of that observed among leuprolide-treated patients (Table 9).

In PEARL II,[11] the manufacturer performed two pre-specified analyses evaluating treatment differences between estradiol levels and the frequency of moderate or severe hot flash self-report using the safety analysis set. At the end of 13 weeks, log-transformed estradiol levels were higher in the ulipristal than in the leuprolide group (difference: 0.52; 95% CI, 0.41 to 0.62). Likewise, hot flashes were less frequent in ulipristal-treated than in leuprolide-treated patients (difference: –28.3%; 95% CI, –40.6% to –14.6%). It should be noted, however, that patients assigned to leuprolide treatment were not provided with add-back hormonal therapy to mitigate the adverse effects of estrogen deprivation from GnRH agonist therapy.[11]

TABLE 8: KEY EFFICACY OUTCOMES

Outcome[a]		PEARL I		PEARL II	
		UA 5 mg	PB	UA 5 mg	LA 3.75 mg
QUALITY OF LIFE/SYMPTOM CONTROL					
***UFS-QoL**, change from baseline to week 13*					
Symptom severity score[b]		NR	NR	–28.2	–27.2
Difference (95% CI)		NR		–1.0 (–10.4 to 8.4)	
HRQoL total score[b]		NR	NR	20.3	17.8
Difference (95% CI)		NR		2.5 (–7.3 to 12.3)	
***Measurement of Discomfort Due to Uterine Fibroids Questionnaire**, change from baseline to week 13*					
Median		–9.0	–6.0	NR	NR
Difference (95% CI)		–4.0 (–6.0 to –1.0)		NR	
***SFMPQ**, change from baseline to week 13*					
A (SFMPQ)[c]		–5.0	–2.5	–5.0	–5.5
Difference (95% CI)		–2.0 (–4.0 to 0.0)		0.2 (–2.0 to 3.0)	
B (VAS)[c]		–30.0	–16.5	–31.0	–32.0
Difference (95% CI)		–12.0 (–25.0 to 1.0)		4.0 (–5.0 to 14.0)	
C (PPI)[c]		–1.0	–1.0	–1.0	–1.0
Difference (95% CI)		0.0 (0.0 to 1.0)		0.0 (–1.0 to 0.0)	
SURGICAL					
Number of patients *not* proceeding to surgery after treatment, n (%)		61 (64.2)	35 (72.9)	52 (55.9)	50 (53.8)
Number of patients switched to less invasive surgeries, n (%)		65 (69.9)	37 (77.1)	57 (62.0)	55 (59.1)
CONTROL OF BLEEDING					
% of patients who achieved PBAC score < 75 at week 13; difference (95% CI)	ITT	91.5	18.8	89.8	88.8
		72.7 (55.1 to 83.2)		1.0 (–9.4[d])	
	PP	92.9	20.0	90.3	89.1
		72.9 (54.6 to 83.8)		1.2 (–9.3[d])	

Outcome[a]	PEARL I		PEARL II	
	UA 5 mg	PB	UA 5 mg	LA 3.75 mg
% of patients in amenorrhea at week 13	73.4	6.3	75.3	80.4
Difference (95% CI)	67.2 (50.2 to 77.0)		–5.2 (–18.7 to 8.6)	
Time to achievement of amenorrhea (i.e., PBAC ≤ 2), median days (95% CI)[12e]	NR	NR	8 (6 to 15)	23 (14 to 28)
REVERSAL OF ANEMIA, IF PRESENT				
***Hematologic parameters**, change from baseline to week 13*				
Hgb[b] (g/dL)	4.1	3.1	0.5	0.5
	0.9 (0.4 to 1.4)		–0.0 (–0.3 to 0.3)	
Hct[b] (%)	10.0	7.4	1.6	1.6
	2.6 (1.0 to 4.1)		–0.0 (–0.9 to 0.8)	
Ferritin[b] (mcg/L)	26.1	21.4	2.2	2.8
	4.8 (–4.4 to 13.9)		–0.6 (–6.2 to 5.0)	
% of patients in whom Hgb rose > 12 g/dL at week 13	85.3	77.1	77.4	76.3
MYOMA VOLUME, *change from screening to week 13*				
% change in total myoma volume[c]	–21.2	3.0	NR	NR
Difference (95% CI)	–22.6 (–36.1 to –8.2)		NR	
Log_{10} change in total myoma volume	–0.13	–0.05	NR	NR
Difference (95% CI)	–0.08 (–0.17 to 0.01)		NR	
Log_{10} change in three largest myomas	NR	NR	–0.18	–0.27
Difference (95% CI)	NR		0.09 (–0.00 to 0.18)	
UTERINE VOLUME, *change from screening to week 13*				
% change in uterine volume[c]	NR	NR	–20.4	–47.1
Log_{10} change in uterine volume[b]	–0.07	0.01	–0.08	–0.25
Difference (95% CI)	–0.08 (0.13 to –0.03)		0.17 (0.10, to 0.24)	

CI = confidence interval; Hct = hematocrit; Hgb = hemoglobin; HRQoL = health-related quality of life; ITT = intention-to-treat analysis; LA = leuprolide acetate; LS = least square; NR = not reported; PB = placebo; PBAC = pictorial bleeding assessment chart; PP = per-protocol analysis; PPI = present pain intensity; SFMPQ = Short-form McGill Pain Questionnaire; UA = ulipristal acetate; UFS-QoL = Uterine Fibroid Symptom and Health-related Quality of Life; VAS = visual analogue scale.
Note: The 10 mg group was not presented as it is not an approved dose.
[a]Outcomes identified as important to the review (see Section 2.2.1 for review protocol).
[b]Adjusted LS mean.
[c]Median.
[d]Lower confidence limit; a value greater than the pre-specified non-inferiority margin of –20% demonstrates non-inferiority.[11]
[e]Exploratory analysis; no formal statistical testing performed.[12]
Unless otherwise specified, data for PEARL I are presented using the ITT analysis set, while data for PEARL II are presented using the PP analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

3.7.2 SAEs

SAEs were infrequent overall and similar between ulipristal and comparator groups in both PEARL I (2.1% versus 4.2%) and PEARL II (5.2% versus 4.0%), with no particular pattern of concentration (Table 9).

3.7.3 WDAEs

WDAEs were also infrequent and without particular pattern. No WDAEs occurred in PEARL I, while in PEARL II, one (1.0%) WDAE occurred in the ulipristal group and five (5.0%) were recorded in the leuprolide group (Table 9).

3.7.4 Mortality

There were no deaths recorded during the conduct of PEARL I or PEARL II.

3.7.5 Notable Harms

The clinical expert consulted by CDR identified two harms of interest: VTE and endometrial hyperplasia or carcinoma. There were no reports of VTE in either PEARL I or II. In PEARL I, there were no diagnoses of endometrial hyperplasia or malignant neoplasm at week 13.[10] In PEARL II, there was one diagnosis of hyperplasia of a simple, non-atypical nature at week 13.[11]

TABLE 9: HARMS

	PEARL I		PEARL II	
	UA (N = 95)	PB (N = 48)	UA (N = 97)	LA (N = 101)
AEs				
Subjects with ≥ 1 AEs, N (%)	47 (49.5)	22 (45.8)	75 (77.3)	85 (84.2)
Most common AEs (≥ 3%)				
Hot flash[a]			25 (25.8)	66 (65.3)
Headache	4 (4.2)	2 (4.2)	25 (25.8)	29 (28.7)
Procedural pain			9 (9.3)	9 (8.9)
Nasopharyngitis	3 (3.2)	0	6 (6.2)	2 (2.0)
Nausea			6 (6.2)	6 (5.9)
Anemia			5 (5.2)	5 (5.0)
Pharyngitis			5 (5.2)	2 (2.0)
Back pain			4 (4.1)	4 (4.0)
Breast pain			4 (4.1)	2 (2.0)
Dysmenorrhea	0	2 (4.2)	4 (4.1)	2 (2.0)
Fatigue			4 (4.1)	3 (3.0)
Hypercholesterolemia	3 (3.2)	1 (2.1)	4 (4.1)	1 (1.0)
Vertigo			4 (4.1)	3 (3.0)
Abdominal pain	2 (2.1)	2 (4.2)	3 (3.1)	9 (8.9)
Abdominal pain, upper			3 (3.1)	5 (5.0)
Constipation	4 (4.2)	1 (2.1)	3 (3.1)	1 (1.0)
Pelvic pain			3 (3.1)	3 (3.0)
Arthralgia			2 (2.1)	3 (3.0)
Diarrhea			2 (2.1)	3 (3.0)
Influenza			2 (2.1)	5 (5.0)
Insomnia			2 (2.1)	5 (5.0)
Migraine			2 (2.1)	3 (3.0)

	PEARL I		PEARL II	
	UA (N = 95)	PB (N = 48)	UA (N = 97)	LA (N = 101)
Muscle spasms			2 (2.1)	3 (3.0)
Hyperhidrosis			1 (1.0)	3 (3.0)
Vomiting			1 (1.0)	4 (4.0)
Acne			0	5 (5.0)
Vaginal infection			0	3 (3.0)
Hypertriglyceridemia	3 (3.2)	1 (2.1)		
Pyrexia	3 (3.2)	2 (4.2)		
SAEs				
Subjects with ≥ 1 SAEs, N (%)	2 (2.1)	2 (4.2)	5 (5.2)	4 (4.0)
Most common SAEs (≥ 1%)				
Headache			1 (1.0)	0
Operative hemorrhage			1 (1.0)	0
Post-procedural complication			1 (1.0)	0
Sarcoma			1 (1.0)	0
Thyroid cancer			1 (1.0)	0
Choriomeningitis, lymphocytic			0	1 (1.0)
Lung infection			0	1 (1.0)
Wound hemorrhage			0	1 (1.0)
Uterine hemorrhage	1 (1.1)	0	0	1 (1.0)
Ovarian hemorrhage	1 (1.1)	0		
Breast cancer	0	1 (2.1)		
Uterine leiomyoma	0	1 (2.1)		
WDAEs				
WDAEs, N (%)	0	0	1 (1.0)	5 (5.0)
DEATHS				
Number of deaths, N (%)	0	0	0	0
NOTABLE HARMS				
VTE	NR	NR	NR	NR
Endometrial hyperplasia	0	0	1 (1.0%)	0
Endometrial carcinoma	0	0	0	0

AE = adverse event; GnRH = gonadotropin-releasing hormone; LA = leuprolide acetate; N = population; NR = not reported; PB = placebo; SAE = serious adverse event; UA = ulipristal acetate; VTE = venous thromboembolism; WDAE = withdrawal due to adverse event.

[a]Pre-specified safety analysis in PEARL II: Hot flashes were less frequent in ulipristal-treated than in leuprolide-treated patients (difference: –28.3%; 95% CI, –40.6% to –14.6%). It should be noted, however, that patients assigned to leuprolide treatment were not provided add-back hormonal therapy to mitigate the adverse effects of estrogen deprivation from GnRH agonist therapy.[11]

Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was drawn from two phase III (PEARL I, n = 144; and PEARL II, n = 204) double-blind, randomized, controlled (placebo — PEARL I, active comparator [leuprolide] — PEARL II) trials, comprising 348 adult women of reproductive age with moderate to severe signs or symptoms from UFs, who were eligible for surgical intervention. Both trials consisted of a 5 mg and 10 mg treatment group; however, for this review, the 10 mg ulipristal treatment group was dropped as it is not a Health Canada–approved dose. PEARL II was a non-inferiority trial with double-dummy component. Inclusion and exclusion criteria were comparable between trials with the exception of anemia, which was a specific inclusion criterion in PEARL I, but not PEARL II. For both trials, the primary efficacy outcome was the percentage of patients with a reduction in uterine bleeding as determined by a PBAC score < 75 at 13 weeks. In addition, PEARL I considered the change in total fibroid volume from screening to week 13 as a co-primary efficacy outcome. Both trials were designed as 13-week trials (end of treatment) with a final visit at week 17, four weeks after stopping study medication. Planned surgical intervention was then completed, switched, or cancelled at the discretion of each site's clinical investigator following study medication cessation; only exploratory efficacy outcomes are available for the post-treatment period, which ran for up to an additional six months (i.e., 38 weeks in total).

PEARL I and II were generally well described and conducted; however, the trials had important limitations. The trials were not designed to specifically assess surgical outcomes instead of surrogate markers (i.e., menstrual bleeding using the PBAC), despite the former's high relevance to the therapeutic area. Quality of life and control of symptoms were important outcomes identified from the patient input received for this submission and were ranked the highest in the hierarchy of outcomes identified for this systematic review. However, the effect of ulipristal on symptom severity and HRQoL are unclear, given it was only statistically significantly superior to placebo on the not yet validated Measurement of Discomfort Due to Uterine Fibroids Questionnaire.

In PEARL II, despite the added rigour of a double-dummy design, it is uncertain to what extent blinding may have been compromised given the higher incidence of well-documented menopausal adverse effects associated with GnRH agonist therapy.[16] The non-inferiority margin of 20% used in PEARL II was a clinical margin, which although considered reasonable by the clinical expert involved in the review, could not be evaluated against efficacy data from published trials.

There is also some uncertainty as to the clinical relevance of the primary efficacy outcome for both trials, the proportion of patients in whom bleeding was controlled by the end of the study as determined by a score of < 75 on the PBAC. Although the PBAC is a validated instrument for assessing uterine blood loss in clinical trials, it is not used universally in clinical practice, and it becomes less well correlated with menstrual blood loss with higher volumes of blood loss.[8] Given that the women enrolled in the trials were determined to have levels of menorrhagia well above the PBAC threshold for menorrhagia (i.e., > 100), it is unclear to what extent observed changes in PBAC scores, especially changes in higher scores, correlate with changes in blood loss, let alone those occurring as a function of treatment. Nonetheless, control of bleeding (PBAC < 75) was achieved in $\geq$ 90% of ulipristal-treated patients in both trials at week 13. No information regarding the MCID with the PBAC has been published.

It is also uncertain how well ulipristal compares with other hormonal and non-hormonal therapies, as no other comparative trials were identified from the literature. It should be noted, however, that aside from ulipristal, none of the other currently used drugs in the management of UFs have a Health Canada indication for this condition. Moreover, no contemporary Canadian clinical practice guidelines on the management of UFs exist, although such guidelines are in the process of being updated, according to the clinical expert involved in the review.

The populations studied in PEARL I and II did not include North American patients; moreover, black women, who are disproportionately affected by UFs, were not studied in PEARL I owing to a failure in recruitment, and made up less than 10% of the population in PEARL II.

4.2 Interpretation of Results

4.2.1 Efficacy

The systematic review protocol, in consideration of patient input submitted, identified quality of life and symptom control as key efficacy outcomes. No statistically significant differences between treatments were identified on these outcomes, except on the not yet validated Measurement of Discomfort Due to Uterine Fibroids (favouring ulipristal treatment), which was used in PEARL I. In PEARL II, both treatment groups showed similar improvements in quality of life and symptom control from baseline; the lack of statistically significant differences between groups is consistent with what would be expected from the non-inferiority trial design. Although there was a similar improvement in UFS-QoL scores between treatment groups in PEARL II, the instrument was not employed in PEARL I, and so the superiority of ulipristal over placebo on this measure has not been established. Likewise, the SFMPQ, a well-known pain questionnaire, was used in both PEARL I and II; although a similar improvement in SFMPQ scores was noted between treatment groups in PEARL II, the superiority of ulipristal over placebo was not demonstrated in PEARL I — a finding that may be attributed to having enrolled patients with mild or no pain symptoms at baseline. The uncertain effect of ulipristal on quality of life and symptom control is notable given the reported large difference between ulipristal and placebo with respect to the proportion of patients achieving a PBAC score < 75 (difference: 72.7%; 95% CI, 55.1% to 83.2%). The absence of a difference in HRQoL favouring ulipristal over leuprolide in PEARL II is also somewhat surprising because of the expected negative impact of leuprolide adverse effects (i.e., medical menopause).

The role for the pharmacologic management of UFs among women who are eligible for surgery is multifactorial: preoperative control of symptoms; improvement of the overall health of patients prior to surgery (i.e., correct anemia, improve QoL); reduction of fibroid size preoperatively, ideally minimizing invasiveness without compromising safety; and improvement of surgical outcomes and safety by reducing intraoperative bleeding.[14] Hence, the aforementioned lack of comparative data on surgical outcomes is an important limitation of both ulipristal trials, as there is no direct evidence that use of ulipristal delays the need for surgery or improves surgical outcomes and safety.

The primary efficacy outcome for both PEARL I and II was the percentage of patients with a PBAC score < 75 at week 13, which was how the trials defined a reduction in uterine bleeding. In PEARL I, a statistically significantly greater proportion of patients treated with ulipristal compared with placebo achieved a PBAC score < 75 at week 13 (difference: 72.7%; 95% CI, 55.1% to 83.2%). In PEARL II, there were no statistically significant differences between ulipristal and leuprolide groups in the primary (PP) analysis of the proportion of patients who achieved a PBAC score < 75 at week 13 (difference: 1.2%; 95% LCL, –9.3%) or in the ITT analysis (difference: 1.0%; 95% LCL, –9.4%). Therefore, ulipristal was found to be non-inferior to leuprolide based on the pre-specified non-inferiority margin of –20%. However, as mentioned

previously, there is a degree of uncertainty as to the clinical relevance of this result, based on the corresponding equivocal findings from the quality of life and symptom control data and the PBAC's apparent lack of correlation with menstrual blood loss at higher volumes of blood loss.[8] As well, the non-inferiority margin used in PEARL II was clinically based and not verified in the literature, although discussion with the clinical expert involved in the review indicated this was a reasonable margin to use. Nonetheless, in PEARL I, a higher proportion of patients treated with ulipristal compared with placebo were in amenorrhea (PBAC $\leq$ 2) at week 13 (difference: 67.2%; 95% CI, 50.2% to 77.0%); in PEARL II, there was no difference between ulipristal and leuprolide on this outcome (difference: –5.2%; 95% CI, –18.7% to 8.6%). Moreover, the effect on bleeding appeared earlier in the course of treatment with ulipristal versus leuprolide; the time to amenorrhea took a median of eight days (95% CI, six days to 15 days) in the ulipristal group, while leuprolide-treated patients took a median of 23 days (95% CI, 14 days to 28 days) to achieve amenorrhea.[12] However, this was an exploratory analysis without formal statistical testing in PEARL II. It is also difficult to contextualize these results as trials of GnRH agonists for UFs have focused on surgical outcomes instead of symptom management.[7]

Although anemic at baseline, a majority of patients in PEARL I were not anemic after 13 weeks of treatment (ulipristal, 85.3% versus placebo, 77.1%); the pattern was similar in PEARL II (ulipristal, 77.4% versus leuprolide, 76.3%), where patients did not have to be anemic for enrolment in the trial. However, the effect of disparate iron supplementation, potentially favouring ulipristal, should be considered when interpreting this outcome.

The change in total fibroid volume from screening to week 13 was a co-primary end point in PEARL I, the findings of which were somewhat inconsistent: while a statistically significant reduction in total myoma volume was observed from screening to week 13 favouring ulipristal treatment (median difference: –22.6%; 95% CI, –36.1% to –8.2%), no statistically significant differences were detected when the raw data were log-transformed. However, the clinical impact of this result on surgical outcomes was not studied in either trial; of note, a large number of surgeries were not completed as planned in the ulipristal and comparator groups in both PEARL I (65.6% versus 72.9%, respectively) and II (55.9% versus 53.8%, respectively) and the reasons for cancelling surgery were not provided. In the six months (i.e., up to week 38) following treatment cessation, there was some suggestion of persistence of myoma volume reduction in PEARL II (–44.8% versus –16.5%), but not PEARL I (–0.3% versus 3.8%), among patients previously treated with ulipristal, but who did not undergo hysterectomy or myomectomy.[10,11]

Contextualizing these findings in terms of ulipristal's comparative efficacy with other hormonal and non-hormonal agents is limited by there being no such trials identified from the literature.

4.2.2 Harms

There were no deaths reported in either trial. AEs were more common overall in PEARL II than in PEARL I, where 80.8% and 48.3% of patients, respectively, experienced one or more AEs. In PEARL I, the frequency of AEs was low and the distribution unremarkable. For ulipristal-treated patients, headache (4.2% versus 4.2% for placebo) and constipation (4.2% versus 2.1% for placebo) were the most common AEs in PEARL I. In PEARL II, hot flashes (ulipristal, 25.8% versus leuprolide, 65.3%) and headache (ulipristal, 25.8% versus leuprolide, 28.7%) were the most common AEs. It should be stated that no hormonal add-back therapy was administered during the trial to leuprolide-treated patients in order to mitigate the effects of estrogen deprivation, such as hot flashes. It is also interesting to note the differential frequency of hot flashes that occurred between PEARL I and II in ulipristal-treated patients: in PEARL I, the frequency was less than 3%, while in PEARL II it was 25.8%. One of the purported advantages of ulipristal therapy is avoidance of adverse effects arising from estrogen deprivation

(e.g., hot flashes), which are often associated with GnRH agonist therapy as a consequence of its mechanism of action. Patients in PEARL I were not provided with adverse effect information about the risk of hot flashes from treatment, which may partly explain the lower frequency of hot flashes observed in the ulipristal group in PEARL I compared with PEARL II. SAEs were infrequent overall and similar between ulipristal and comparator groups in both PEARL I (2.1% versus 4.2%, respectively) and PEARL II (5.2% versus 4.0%, respectively) with no particular pattern of concentration. WDAEs were also infrequent and without particular pattern. Two harms of interest were pre-specified for the systematic review: VTE and endometrial hyperplasia or carcinoma. There were no reports of VTE in either PEARL I or II. In PEARL I, there were no diagnoses of endometrial hyperplasia or malignant neoplasm at the end of the treatment period (i.e., week 13),[10] while in PEARL II, there was one diagnosis of hyperplasia of a simple, non-atypical nature at week 13.[11] In the six months (i.e., up to week 38) following treatment cessation, investigators did not identify any malignant endometrial changes in either trial, and indicated that a majority of patients had experienced a reversal of initial, non-physiologic endometrial changes after stopping treatment.[10,11]

4.3 Other Considerations

Based on discussion with the clinical expert involved in the review, the following potential off-label uses of ulipristal were identified.

4.3.1 Emergency Contraception

The medication is in a class of drugs that have been used in different therapeutic areas, including emergency contraception. However, this indication is available outside Canada and the corresponding dose is six times higher (30 mg UA) than the daily dose approved for UFs. Given this and the availability of less expensive and easier to obtain alternatives for emergency contraception in Canada, the clinical expert stated that ulipristal was unlikely to be used as emergency contraception.

4.3.2 Heavy Menstrual Bleeding

Ulipristal might be used for the control of acute heavy menstrual bleeding. However, the clinical expert stated that this too was unlikely — at least in the near future — unless the post-market experience confirms this among Canadian providers.

5. CONCLUSIONS

In two phase III RCTs, 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 agonist (i.e., leuprolide) therapy in PEARL II; hence, ulipristal was found to be non-inferior to leuprolide, based on the pre-specified non-inferiority 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 and SAEs. 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.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by Canadian Agency for Drugs and Technologies in Health (CADTH) staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Groups Supplying Input

The UnHysterectomy is a virtual community consisting of the author and followers of the UnHysterectomy website, blog, book, online radio and television program, Facebook, and Twitter feeds. The group's mission is to help women share and connect with other sufferers of fibroids, endometriosis, polyps, cysts, and other menstrual disorders and to access the least invasive, most effective medical and surgical treatments available. The Facebook page has more than 1,100 members and there are 150 Twitter followers. More than 90% of members suffer from fibroids.

Canadian Women with Fibroids (CANFib) is an online group of women frustrated with dealing with fibroids. Their conviction is that too much time has passed and there are too many sufferers to still have surgeries be the only real treatment options available.

Both organizations declare no conflict regarding funding or the compilation of their submissions.

2. Condition and Current Therapy Related Information

Information was gathered using previously conducted interviews of patients, gynecologists, and other health care professionals found through traditional and social media, referrals, and online groups.

Fibroids are non-cancerous masses that grow within the uterine wall and affect approximately one in four women of reproductive age worldwide. Fibroids can lie dormant and cause no symptoms or can be extremely painful, growing up to the size of an orange or even a watermelon. These tumours cause mental, physical, emotional, financial, and sexual side effects, including pain, pressure, extreme blood loss during menstruation, the need for emergency blood transfusions, debilitating exhaustion, anemia, cognitive impairment such as memory loss and confusion, lost wages, greater-than-average expenses for menstrual supplies, adult diapers, medications, and cleaning expenses, and quality of life costs such as missed family life and social engagements. It is not unusual for women with fibroids to call in sick one to five days per month and change their supplies every 60 to 90 minutes during the peak of the menstrual cycle. Many women, particularly after a single embarrassing incident such as suddenly being covered in blood in a bank line, choose to stay at home rather than risk the pain and embarrassment of an accident while out.

Perhaps the most heartbreaking side effect of fibroids is infertility. Many women, some as young as their teens or twenties, have chosen and continue to choose hysterectomy out of sheer desperation to relieve their symptoms, before having had the chance to have children. Despite the alarming nature of excessive bleeding (especially in public), the intense pain, frightening abdominal bulges, and having to give up social outings, hobbies, exercising, or even walking, mentioning their symptoms to a doctor often elicits nothing more than the repeated suggestion to have a hysterectomy, and many patients report that their doctors either do not discuss or they dismiss other options, including hormone treatments, completely. Some patients reported having to travel to the US and pay out of pocket to access less invasive surgeries with the potential to retain or restore fertility.

On a continuum from least to most invasive, current therapies for UFs include watchful waiting; over-the-counter medications, such as ibuprofen, to lessen pain and lighten flow; the blood-thickening product tranexamic acid; hormone therapy such as leuprolide, intrauterine devices, or other birth control methods to stop menstruation; focused ultrasound; uterine artery embolization; dilation and curettage; hysteroscopy; endometrial ablation; myomectomy; and hysterectomy.

Surgically speaking, fibroids account for more hysterectomies in Canada than any other condition, more than doubling the number performed for gynecological cancers. Of the 50,000 hysterectomies performed in Canada in 2010, 33% were for fibroids. A lack of training and awareness of newer medical and surgical treatment options means that in most cases, these hysterectomies could have been avoided through less expensive, risky, invasive, and painful means. Additionally, despite national guidelines from the Society of Obstetrician and Gynaecologists recommending laparoscopic or vaginal hysterectomies, the majority performed in Canada continue to be done through deep, invasive abdominal cuts requiring general anaesthetic and hospitalization at a cost of $192 million a year.

Women who had used leuprolide reported unpleasant side effects such as hot flashes, mood swings, night sweats, and other effects associated with the medication's mimicking of menopause.

While most patients are their own caregivers, spouses and loved ones often have to provide extra assistance with child care, errands, housework, and financial support. Studies show that women with heavy menstrual bleeding spend $5,000 a year each on supplies and lost wages. Additionally, intimate relationships are also affected and over a period of years, this can lead to mood disorders and sexual side effects for both partners. The sheer "ongoingness" of fibroids can cause strain and stress for family life. Some patients reported relationships ending due to infertility, frustration, inability to cope with a partner in frequent pain or who is difficult to deal with, and lack of intimacy, which can lead to absence or infidelity.

Although heavy menstrual bleeding from fibroids may be considered "only" a quality of life issue, it is worth noting that a 2009 study by the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, US, found that the level of function among women suffering from heavy menstrual bleeding was similar to patients who are visually impaired due to age-related macular degeneration, are entering cardiac rehabilitation after a heart attack or bypass surgery, or have malignant esophageal dysphagia. An unmet need is a drug therapy to treat the fibroids themselves rather than attempting to control symptoms such as pain and bleeding.

3. Related Information about the Drug Being Reviewed

No patients reported direct experience with Fibristal, as clinical trials did not take place in Canada. Based on online sources and anecdotes from patients in the United Kingdom, patients who are aware of ulipristal acetate (UA) expect it to reduce the size of fibroids, to reduce symptoms such as pain and bleeding, and to become another accepted preoperative treatment option. While patients expect Fibristal to cause fewer side effects than the less site-specific hormone suppressor leuprolide, they are willing to tolerate some side effects and non-permanent adverse events for an improvement in their symptoms. Many feel that any improvement would be adequate and are desperate to try UA to improve their mental, physical, emotional, sexual, and financial quality of life.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to 2013 June 4 Ovid MEDLINE In-Process & Other Non-Indexed Citations Ovid MEDLINE Daily and Ovid MEDLINE 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 4 2013
Alerts:	Weekly search updates until October 16 2013
Study Types:	No filters used
Limits:	No date or language limits used.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
.ti	Title
.ab	Abstract
.ot	Original title
.nm	Name of substance word
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.rn	CAS registry number
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	ulipris* or esmya* or fibristal* or va-2914 or va2914 or 6J5J15Q2X8).ti,ab,ot,sh,rn,hw,nm.
2	159811-51-5.rn.
3	1 or 2
4	3 use pmez
5	*ulipristal/
6	*ulipristal acetate/
7	5 or 6
8	(ulipris* or esmya* or fibristal* or va-2914 or va2914 or 6J5J15Q2X8).ti,ab.
9	7 or 8
10	9 use oemezd
11	4 or 10
12	remove duplicates from 11

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and other)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	July 2013
Keywords:	Included terms for Fibristal and Uterine fibroids
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Nieman LK, et al. Fertil Steril. 2011 Feb;95(2):767-72	Wrong dose

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: UFS-QOL — CHANGE FROM BASELINE TO WEEK 13

UFS-QoL Component		Treatment Group	N	Adjusted LS Mean	Treatment Difference (95% CI)
Symptom severity	PEARL I[a]	UA	NR	NR	NR
		PB	NR	NR	
	PEARL II[b]	UA	53	–28.2	–1.0 (–10.4 to 8.4)
		LA	46	–27.2	
HRQoL total score	PEARL I[a]	UA	NR	NR	NR
		PB	NR	NR	
	PEARL II[b]	UA	53	20.3	2.5 (–7.3 to 12.3)
		LA	46	17.8	

CI = confidence interval; HRQoL = health-related quality of life; LA = leuprolide acetate; LS = least square; N = population; NR = not reported; PB = placebo; UA = ulipristal acetate; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 11: SFMPQ — CHANGE FROM BASELINE TO WEEK 13

SFMPQ Component		Treatment Group	N	Median	Treatment Difference (95% CI)
A (SFMPQ)	PEARL I[a]	UA	95	–5.0	–2.0 (–4.0 to 0.0)
		PB	48	–2.5	
	PEARL II[b]	UA	93	–5.0	0.2 (–2.0 to 3.0)
		LA	93	–5.5	
B (VAS)	PEARL I[a]	UA	95	–30.0	–12.0 (–25.0 to 1.0)
		PB	48	–16.5	
	PEARL II[b]	UA	93	–31.0	4.0 (–5.0 to 14.0)
		LA	93	–32.0	
C (PPI)	PEARL I[a]	UA	95	–1.0	0.0 (0.0 to 1.0)
		PB	48	–1.0	
	PEARL II[b]	UA	93	–1.0	0.0 (–1.0 to 0.0)
		LA	93	–1.0	

CI = confidence interval; LA = leuprolide acetate; N = population; PB = placebo; SFMPQ = Short-form McGill Pain Questionnaire; PPI = present pain intensity; UA = ulipristal acetate; VAS = visual analogue scale.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 12: MEASUREMENT OF DISCOMFORT DUE TO UTERINE FIBROIDS QUESTIONNAIRE — CHANGE FROM BASELINE TO WEEK 13

Change from Baseline	PEARL I		PEARL II	
	UA 5 mg (N = 95)	PB (N = 48)	UA 5 mg	LA 3.75 mg
Median	–9.0	–6.0	NR	NR
Difference 95% CI *P* value	–4.0 (–6.0 to –1.0) 0.001		NR	

CI = confidence interval; LA = leuprolide acetate; N = population; NR = not reported; PB = placebo; UA = ulipristal acetate.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 13: ANALYSIS OF SURGERY

Surgical Outcome		Treatment Group	N	Proportion of Patients, n (%)	Treatment Difference (%) (95% CI)
Surgery cancelled	PEARL I[a]	UA	93	61 (65.6)	–7.3 (–23.8 to 11.6)
		PB	48	35 (72.9)	
	PEARL II[b]	UA	93	52 (55.9)	2.2 (–13.9 to 18.0)
		LA	93	50 (53.8)	
Less invasive surgery	PEARL I[a]	UA	93	65 (69.9)	–7.2 (–22.8 to 11.2)
		PB	48	37 (77.1)	
	PEARL II[b]	UA	92	57 (62.0)	2.8 (–13.0 to 18.4)
		LA	93	55 (59.1)	

CI = confidence interval; LA = leuprolide acetate; n = subpopulation; N = population; PB = placebo; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 14: SUMMARY OF SURGERY

Surgical Procedure, n (%)	PEARL I[a]				PEARL II[b]			
	UA 5 mg		PB		UA 5 mg		LA 3.75 mg	
	Planned	Completed	Planned	Completed	Planned	Completed	Planned	Completed
No surgery		61 (64.2)		35 (72.9)		52 (55.9)		50 (53.8)
Endometrium ablation	1 (1.1)	0	0	0	1 (1.1)	2 (2.2)	0	0
Uterine artery embolization	17 (17.9)	12 (12.6)	8 (16.7)	5 (10.4)	0	0	2 (2.2)	1 (1.1)
Hysteroscopic myomectomy	2 (2.1)	0	0	0	6 (6.5)	3 (3.2)	2 (2.2)	3 (3.2)
Laparoscopic myomectomy	10 (10.5)	3 (3.2)	4 (8.3)	1 (2.1)	17 (18.3)	7 (7.5)	19 (20.4)	9 (9.7)
Laparotomic myomectomy	16 (16.8)	4 (4.2)	6 (12.5)	1 (2.1)	21 (22.6)	15 (16.1)	25 (26.9)	15 (16.1)
Vaginal hysterectomy	4 (4.2)	3 (3.2)	6 (12.5)	0	2 (2.2)	2 (2.2)	1 (1.1)	1 (1.1)
Laparoscopic hysterectomy	11 (11.6)	3 (3.2)	3 (6.3)	0	14 (15.1)	5 (5.4)	15 (16.1)	5 (5.4)
Laparotomic hysterectomy	34 (35.8)	7 (7.4)	21 (43.8)	6 (12.5)	32 (34.4)	6 (6.5)	29 (31.2)	9 (9.7)
Other	0	0	0	0	0	1 (1.1)	0	0
Missing		2 (2.1)		0				
Ovariectomy: left		4 (4.2)		1 (2.1)		2 (2.2)		3 (3.2)
Ovariectomy: right		4 (4.2)		2 (4.2)		3 (3.2)		3 (3.2)

LA = leuprolide acetate; n = subpopulation; N = population; PB = placebo; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 15: PROPORTION OF PATIENTS WITH PBAC SCORE < 75

PBAC Score < 75		Treatment Group	N	Proportion of Patients, n (%)	Treatment Difference (%) (95% CI)
At week 13 (LOCF)	PEARL I[a]	UA	94	86 (91.5)	72.7 (55.1 to 83.2)
		PB	48	9 (18.8)	
	PEARL II[b]	UA	93	84 (90.3)	1.2 (–9.3[c])
		LA	92	82 (89.1)	
	PEARL II[a]	UA	98	88 (89.8)	1.0 (–9.4[c])
		LA	98	87 (88.8)	
Last 28 days under treatment	PEARL I[a]	UA	94	85 (90.4)	67.5 (49.4 to 79.2)
		PB	48	11 (22.9)	
	PEARL II[b]	UA	93	86 (92.5)	3.3 (–6.7[c])
		LA	92	82 (89.1)	
	PEARL II[a]	UA	98	90 (91.8)	3.1 (–6.9[c])
		LA	98	87 (88.8)	

CI = confidence interval; LA = leuprolide acetate; LOCF = last observation carried forward; n = subpopulation; N = population; PB = placebo; PBAC = pictorial bleeding assessment chart; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
[c]Lower confidence limit; a value greater than the pre-specified non-inferiority margin of –20% demonstrates non-inferiority.[11]
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 16: CHANGE IN PBAC SCORE FROM BASELINE TO WEEK 13

Change in PBAC Score		Treatment Group	N	Median	Treatment Difference (95% CI)
Week 13 (LOCF)	PEARL I[a]	UA	95	–328.5	–291.0 (–399.0 to –194.0)
		PB	48	–59.0	
	PEARL II[b]	UA	93	–268.0	6.0 (–54.0 to 63.0)
		LA	93	–273.5	
	PEARL II[a]	UA	98	–260.0	10.0 (–47.0 to 67.0)
		LA	99	–268.0	

CI = confidence interval; LA = leuprolide acetate; LOCF = last observation carried forward; N = population; PB = placebo; PBAC = pictorial bleeding assessment chart; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 17: ANALYSIS OF PATIENTS IN AMENORRHEA AT WEEK 13

Amenorrhea		Treatment Group	N	Patients in Amenorrhea, n (%)	Treatment Difference (%) (95% CI)
Week 13 (LOCF)	PEARL I[a]	UA	94	69 (73.4)	67.2 (50.2 to 77.0)
		PB	48	3 (6.3)	
	PEARL II[b]	UA	93	70 (75.3)	–5.2 (–18.7 to 8.6)
		LA	92	74 (80.4)	

CI = confidence interval; LA = leuprolide acetate; LOCF = last observation carried forward; n = subpopulation; N = population; PB = placebo; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 18: HEMATOLOGY — CHANGE FROM BASELINE TO WEEK 13

Hematologic Parameter[a]		Treatment Group	N	Adjusted LS Mean	Treatment Difference (95% CI)
Hemoglobin (g/dL)	PEARL I[b]	UA	95	4.1	0.9 (0.4 to 1.4)
		PB	48	3.1	
	PEARL II[c]	UA	93	0.5	–0.0 (–0.3 to 0.3)
		LA	93	0.5	
Hematocrit (%)	PEARL I[b]	UA	95	10.0	2.6 (1.0 to 4.1)
		PB	48	7.4	
	PEARL II[c]	UA	93	1.6	–0.0 (–0.9 to 0.8)
		LA	93	1.6	
Ferritin (mcg/L)	PEARL I[b]	UA	95	26.1	4.8 (–4.4 to 13.9)
		PB	48	21.4	
	PEARL II[c]	UA	93	2.2	–0.6 (–6.2 to 5.0)
		LA	93	2.8	

CI = confidence interval; LA = leuprolide acetate; LS = least square; N = population; PB = placebo; UA = ulipristal acetate.
[a]All measured values irrespective of blood transfusions.
[b]Intention-to-treat analysis set.
[c]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 19: CHANGE IN TOTAL MYOMA VOLUME FROM SCREENING TO WEEK 13

Myoma Volume		Treatment Group	N	Median	Treatment Difference (95% CI)
% Change	PEARL I[a]	UA	95	–21.2	–22.6 (–36.1 to –8.2)
		PB	48	3.0	
	PEARL II[b]	UA	NR	NR	NR
		LA	NR	NR	
Log_{10} change	PEARL I[a]	UA	95	–0.13	–0.08 (–0.17 to 0.01)
		PB	48	–0.05	
	PEARL II[b]	UA	NR	NR	NR
		LA	NR	NR	

CI = confidence interval; LA = leuprolide acetate; N = population; NR = not reported; PB = placebo; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 20: CHANGE IN TOTAL VOLUME OF THREE LARGEST MYOMAS FROM SCREENING TO WEEK 13

Myoma Volume		Treatment Group	N	Adjusted LS Mean	Treatment Difference (95% CI)
Log_{10} change	PEARL I[a]	UA	NR	NR	NR
		PB	NR	NR	
	PEARL II[b]	UA	93	–0.18	0.09 (–0.00 to 0.18)
		LA	93	–0.27	
	PEARL II[a]	UA	98	–0.18	0.10 (0.01 to 0.19)
		LA	99	–0.27	

CI = confidence interval; LA = leuprolide acetate; LS = least square; N = population; NR = not reported; PB = placebo; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 21: PROPORTION OF PATIENTS WITH ≥ 25% REDUCTION IN MYOMA, UTERINE VOLUME AT WEEK 13

Outcome		Treatment Group	N	Proportion of Patients, n (%)	Treatment Difference (%) (95% CI)
Myoma volume reduction ≥ 25%	PEARL I[a]	UA	85	35 (41.2)	23.4 (4.1 to 38.7)
		PB	45	8 (17.8)	
	PEARL II[b]	UA	NR	NR	NR
		LA	NR	NR	
Uterine volume reduction ≥ 25%	PEARL I[a]	UA	88	30 (34.1)	27.7 (11.3 to 40.4)
		PB	47	3 (6.4)	
	PEARL II[b]	UA	NR	NR	NR
		LA	NR	NR	

CI = confidence interval; LA = leuprolide acetate; n = subpopulation; N = population; NR = not reported; PB = placebo; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

TABLE 22: CHANGE IN UTERINE VOLUME FROM SCREENING TO WEEK 13

Uterine Volume		Treatment Group	N	Adjusted LS Mean	Treatment Difference (95% CI)
Log_{10} change	PEARL I[a]	UA	95	–0.07	–0.08 (–0.13 to –0.03)
		PB	48	0.01	
	PEARL II[b]	UA	93	–0.08	0.17 (0.10 to 0.24)
		LA	93	–0.25	

CI = confidence interval; LA = leuprolide acetate; LS = least square; N = population; PB = placebo; UA = ulipristal acetate.
[a]Intention-to-treat analysis set.
[b]Per-protocol analysis set.
Sources: PEARL I clinical study report,[10] PEARL II clinical study report.[11]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To assess the validity of measures used in clinical trials assessing either menstrual blood loss or quality of life aspects associated with the presence of uterine fibroids (UFs). The measures assessed were the pictorial bleeding assessment chart (PBAC), the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QoL), the Short-form McGill Pain Questionnaire (SFMPQ), and the Measurement of Discomfort Questionnaire. In addition, minimal clinically important differences (MCIDs) were reported if available.

Findings

Pictorial Bleeding Assessment Chart

The PBAC is a relatively simple semi-quantitative method of assessing cyclic menstrual blood loss.[8,20,21] The chart consists of a series of diagrams that represent a range of bleeding from lightly to heavily soiled tampons, towels, or pads and a grid to mark down when the sanitary protection was changed, and which pictorial category it fell into.[8,20-22] PBAC scores were different depending on the study, ranging from 5 to 545, with higher scores correlating to greater blood loss.[8,22] Cut-off scores differed between studies; however, a PBAC cut-off score of 100 (Appendix 5, Table 23) was generally acceptable, with scores greater than 100 indicating menorrhagia.[8,22] The PBAC does not provide an objective measurement in millilitres, like the gold standard alkaline hematin method.[8,20-22] For the purposes of menstrual blood loss assessment, however, the alkaline hematin method is more time-consuming and requires specialized laboratory assessment.

Three trials reported the PBAC to be valid and reliable in measuring MBL,[8,20,21] while another trial did not.[22] All studies incorporated a main study design whereby sanitary protection was assessed with the PBAC by both patient and gynecologist, both of whose results were then subsequently compared with the alkaline hematin method.[8,20-22] Sensitivity ranged from 83% to 98% and specificity ranged from 64% to 89%.[8,20,21] In addition, the positive likelihood ratio (a positive test > 1 will most likely occur in those with the disease) ranged from 2.5 to 7.8, while the negative likelihood ratio (a negative test < 1 will be less likely to occur in those with the disease) ranged from 0.04 to 0.22.[8,20,21] Zakhareh et al. had two cut-off values (Appendix 5, Table 23) and determined that the PBAC cut-off score of 150 was associated with the best precision, kappa 0.593 (95% CI, 0.480 to 0.687).[21] The other trials used a PBAC cut-off score of 100.[8,20,22] Additionally, Higham et al. observed that greater than two standard deviations of the differences were associated with PBAC scores greater than 150, thus showing less reliability using a higher cut-off.[8]

The study by Reid et al. did not report the PBAC to be a valid method for assessing MBL in symptomatic women.[22] They found that, at its worst, a ten-fold difference in the estimation of blood loss using the PBAC could be observed when compared with the alkaline hematin method. In addition, the authors noted a poor correlation between these methods.[22] However, diagnostic odds ratios (DOR) in the trials validating the PBAC ranged from 15.7 to 76.7, while Reid et al.[22] reported it as 2.6. According to Zakhareh et al., this DOR score was low but still indicated an intermediate level of accuracy, suggesting its potential use in clinical practice after improvement, or when used beside other diagnostic tools.[21]

TABLE 23: COMPARISON OF THE PBAC DIAGNOSTIC ACCURACY MEASURES BETWEEN TRIALS

Author, Year	N	Cut-Off Value	MBL of > 80 mL (%)	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio[a]	Negative Likelihood Ratio[a]
Higham et al. 1990[8]	122	100	50	86	89	7.8	0.16
Janssen et al. 1995[20]	288	100	31	98	64	2.7	0.04
Reid et al. 2000[22]	103	100	61	97	7.5	1.1	0.4
Zakherah et al. 2011[21b]	197	100	54	99	39	1.6	0.02
Zakherah et al. 2011[21c]	197	150	54	83	77	3.5	0.22

MBL = menstrual blood loss; N = population; PBAC = pictorial bleeding assessment chart.
[a]Calculated by Zakhareh et al.[21]
[b]Lower cut-off value.
[c]Higher cut-off value.

Two trials additionally assessed the passage of blood clots in order to determine their importance in MBL assessment.[8,20] One trial reported that blood clot passage in women with > 80 mL of MBL appeared to be an important component of menses of higher volumes.[8] In contrast to this, Janssen et al. concluded that assessing blood clots appeared unnecessary in MBL assessment, thus indicating that they need not be added to the PBAC assessment.[20]

Potential limitations of these trials included aspects such as potential falsification of results and patient selection bias. Falsification could occur with any test that a patient uses to assess an outcome; however, Higham et al. noted that, should the clinician be wary of this potential, they could easily collect soiled sanitary protection to ensure honest MBL reporting.[8] Only two trials[20,21] indicated that they included both women potentially suffering from menorrhagia along with healthy volunteers, whereas one incorporated only those women attending a menorrhagia research clinic,[22] and the other did not specify.[8]

The validity and reliability of the PBAC for the determination of MBL was demonstrated in three trials.[8,20,21] The Reid et al. study could not validate the PBAC in women suspected of having menorrhagia;[22] however, they did not incorporate any "normal" controls, thereby potentially incorporating some bias into their observations. In addition, their low DOR appears to provide an intermediate level of accuracy, suggesting that it is still an appropriate method to assess MBL. No MCIDs were identified in the literature search used to accumulate evidence regarding the validity of the PBAC.

Short-form McGill Pain Questionnaire

The SFMPQ was developed as a shortened version of the full McGill Pain Questionnaire (MPQ), comprising a select, small, but representative set of words from the sensory and affective categories of the MPQ. The full MPQ takes five to 20 minutes to administer and primarily consists of a list of words describing pain, of which the patient rates the intensity, based on their feelings at that moment.[23,24] The list of descriptors in the full MPQ was derived from the literature and existing questionnaires, and is sorted into three main categories with words regarding the following: sensory qualities of pain (e.g.,

temporal, thermal); affective qualities of pain (e.g., fear, tension); and evaluative words that describe the subjective overall intensity of the total experience of pain.[23,24]

The SFMPQ takes two to five minutes to administer and includes 15 descriptive words. Eleven are sensory words (including throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and splitting) and four are affective words (including tiring-exhausting, sickening, fearful, and punishing-cruel).[25] Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, and 3=severe. Three pain scores are derived from the sum of the intensity rank values of the words chosen for each category: sensory (range 0–33), affective (range 0–12), and total descriptors or sum of the sensory and affective scores (range 0–45).[25] In addition, a 100 mm visual analogue scale (VAS) and a six-point present pain intensity (PPI) component where 0 = no pain and 5 = excruciating pain are included in the SFMPQ, which provide overall intensity scores.

The MPQ has been extensively studied and found to be valid, reliable, and consistent.[23] Its primary advantages are the magnitude of research supporting its reliability and validity, that it provides data on the quantitative and qualitative aspects of pain, and that it is one of the few instruments available that addresses the multidimensionality of pain.[26] The SFMPQ has been shown to be significantly correlated with the MPQ for scores obtained from patients in obstetrical and post-surgical wards, physiotherapy, and dental departments.[25] No information from our literature search could answer what change in score on the SFMPQ would constitute a MCID.

Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire

The UFS-QoL is a disease-specific questionnaire used to evaluate uterine fibroid symptoms and outcomes from fibroid therapies by assessing their impact on health-related quality of life (HRQoL).[27,28] It consists of an eight-item symptom severity scale and 29 HRQoL items comprising six separate domains: Concern, Activity, Energy/Mood, Control, Self-consciousness, and Sexual Function. A 5-point Likert scale is used for scoring both symptom severity and HRQoL items, 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 to 100 point scale for symptom severity and HRQoL subscales. These score in opposite manners, with higher symptom scores associated with greater symptom severity and higher HRQoL scores associated with better HRQoL.[27,28]

Coyne et al.[27] reported the validity and reliability of the 37-item version of the UFS-QoL Questionnaire in their fibroid treatment group (FTG) (treatment groups were hysterectomy, myomectomy, or uterine fibroid embolization [UFE]) and in a normal control group (NCG). The UFS-QoL method provided similar results to the Short-Form 36 health survey (SF-36) when examining differences between the FTG and NCG at baseline. Subscales of both the UFS-QoL and SF-36 each showed statistically significant differences between groups, with greater symptom severity and lower HRQoL reported in the FTG. With the exception of the mental health subscale of the SF-36 reported by the hysterectomy group (reporting a significantly worse score compared with those patients in the UFE group), no significant differences were observed using any domain of either instrument among the three FTGs at baseline.[27] The UFS-QoL had adequate internal consistency for the NCG, FTG, and three FTGs, with alphas ranging from 0.73 to 0.97 at baseline. In addition, adequate internal consistency was observed at both the six- and 12-month follow-ups, with ranges of 0.77 to 0.99 and 0.78 to 0.97, respectively.[27] No MCIDs were derived from the Coyne et al. study, due to the small number of women who reported worse scores (n = 5) while the rest reported improvements, and an overwhelmingly large percentage of patients (90%) reporting positive responses with a ≥ 20 point reduction in symptom severity. According to the study investigators, this made the estimation of an MCID difficult.[27] A five-point cut-off for improvement was reported as

clinically meaningful in studies that reported on[19] or used[29] the UFS-QoL to assess a change in HRQoL for patients who underwent myomectomy or uterine artery embolization. However, this MCID was formed from expert opinion from these studies and not based on a true derivation of the MCID.

The responsiveness of the UFS-QoL was also assessed in both patients receiving alternate minimally invasive or noninvasive uterine fibroid treatments (including hysteroscopic myomectomy, MRI-guided transvaginal cryotherapy, minilaparotomy myomectomy, and thermal balloon ablation)[27,28] and in those who underwent hysterectomy.[27] Statistically significant improvement in the symptom severity and all HRQoL subscales were observed at both the three- and six-month follow-up in patients who underwent MRI-guided focused ultrasound thermal ablation treatment for uterine fibroids, an experimental procedure.[28] All of the UFS-QoL HRQoL subscales were observed to differentiate between patients who were satisfied with treatment compared with those who were not, and between patients who reported treatment was effective at eliminating symptoms compared with those who did not.[28] In addition, Coyne et al. reported the UFS-QoL was highly responsive to treatment changes in the FTG (no changes were reported in the NCG, as expected) at both the six- and 12-month follow-up periods.[28]

Limitations to the Coyne et al. study include the fact that it was a non-randomized study design with women knowing and selecting their uterine fibroid treatment procedure; that the test-retest analysis was limited to a small sample of women (most belonging to the NCG); and that this study was designed for a five-year follow-up, which was cancelled after one year due to funding issues.[27] The main limitation of the Harding et al. study was the lack of a control group.[28]

The UFS-QoL Questionnaire was observed to be a valid, reliable,[27] and responsive[27,28] method when assessing HRQoL after various treatments in women with uterine fibroids.

Measurement of Discomfort Questionnaire

Created in-house by the manufacturer, the Measurement of Discomfort Questionnaire was derived from the UFS-QoL Questionnaire as a means of managing around the non-availability of the UFS-QoL (or other QoL instrument) to meet the linguistic needs of the PEARL trials. No additional literature was identified regarding its validity or reliability.

APPENDIX 6: SUMMARY OF COMPARATORS

Objective

To summarize the comparative information on standard hormonal therapeutic options used in the treatment of uterine fibroids (UFs).

Findings

A supplemental search was conducted to identify systematic reviews and/or meta-analyses associated with pharmacological treatment (gonadotropin-releasing hormone (GnRH) agonists, combined hormonal contraceptives, progestin-releasing intrauterine systems (IUDs), and progestins) for the treatment of UFs. One systematic review from 2011 was identified that examined pre-treatment with GnRH agonists prior to laparoscopic myomectomy,[7] and another from 2010 examined the potential increased risks of uterine bleeding and expulsion risks associated with levonorgestrel intrauterine device (levonorgestrel IUD) use in women with UFs.[30] No literature on combined hormonal contraceptives or progestins for uterine fibroid treatment was identified from this search. Of note, none of the aforementioned classes of drugs has a Health Canada indication for treating UFs.

The AMSTAR assessment tool for systematic reviews was used to evaluate the quality of the included systematic reviews. The AMSTAR was used by one clinical reviewer to assess the quality of the included systematic reviews. Both reviews had high scores on all of the assessment criteria except the following: list of exclusion studies provided,[7,30] duplicate study selection or data extraction,[30] publication bias,[30] and statement of conflicts of interest.[30]

Gonadotropin-releasing Hormone Agonists

GnRH agonists are used in the treatment of UFs to aid in anemia correction and reduce uterine and fibroid volume in a reversible fashion by inducing a state of artificial menopause.[17] They are often used in a pre-surgical setting, but are recommended only for short-term (three to four months) use.[7,17] The most problematic adverse effects are menopausal symptoms, such as hot flashes and loss of bone mineral density.[17,31]

The systematic review consisted of three randomized controlled trials (RCTs) with 171 patients, all of which compared GnRH agonists with placebo or no treatment in pre-surgical patients scheduled to receive laparoscopic myomectomy.[7] The a priori outcomes of interest included operative time, intraoperative blood loss, need for blood transfusions, post-operative hemoglobin, and intraoperative complications. Reductions in intraoperative bleeding and improvement in post-operative hemoglobin concentrations were observed (via meta-analysis) in patients pretreated with GnRH agonists. The existence of a discrepancy between the intraoperative blood loss (~60 mL) and the moderate difference in post-operative hemoglobin concentrations (1.15 g/dL) was noted. Explanations for this discrepancy were possible errors in blood measurement due to incomplete aspirations of intra-abdominal fluid, or increased intraoperative bleeding in the non-pre-treatment group when compared with the GnRH agonist group. With regard to the primary outcome of interest, the authors reported no difference in laparoscopic myomectomy operative times between GnRH agonist and the non-pre-treatment arm.[7]

The systematic review was found to be of high quality and was missing only the excluded study list criteria of the AMSTAR tool. Source selection bias (only published English studies were selected) was postulated to be a potential limitation; however, the magnitude and direction of the effects on surgical outcomes with GnRH agonist pre-treatment likely rendered the meta-analysis results valid.[7] In addition,

the limited number of eligible studies identified and their lack of power to detect differences in less common outcomes were potential limitations.[7] Finally, all included studies originated from Italy. Even though this could have compromised external validity, all included studies contained detailed descriptions of both interventions and populations, which were found to correlate well with similar studies reported by other centres.[7]

Intrauterine Devices

The levonorgestrel IUD is one of the hormonal medication options used in the treatment of UFs. Levonorgestrel IUD use has been associated with decreases in uterine size, menstrual blood loss, and myoma volume, and increases in hemoglobin and serum follicle-stimulating hormone.[4] Of the more prevalent adverse effects correlated with levonorgestrel IUD, approximately 68% of women experience bleeding disturbances with its use.[4] In addition, expulsion of the device from women with large myomas and distorted uterine cavities has been observed.[4]

Two systematic reviews were identified that examined the use of the levonorgestrel IUD in women with UFs: one examined the potential risk for uterine bleeding post levonorgestrel IUD insertion, and the other the risk for levonorgestrel IUD expulsion.[30] Eleven non-comparative studies examined uterine bleeding outcomes associated with levonorgestrel IUD insertion (n = 393); however, only eight of these studies observed intrauterine bleeding before and after levonorgestrel IUD insertion in women with UFs (n = 223 patients). Some of the women in these eight studies also had menorrhagia (range 39% to 100%). All 11 of the included studies demonstrated reductions in MBL with levonorgestrel IUD insertion and decreased blood loss associated with continued levonorgestrel IUD use. Evidence from 10 studies also demonstrated no increase in MBL with levonorgestrel IUD use.[30] The authors noted several limitations. All included studies had moderate to small sample sizes, with no comparison group of women with UFs not using levonorgestrel IUD; the analysis of MBL was not assessed with the validated PBAC in six studies, and three studies included women with menorrhagia without UFs as part of their samples and did not subsequently stratify for fibroids.[30] In addition, exclusions of women who underwent hysterectomies or withdrew from the trials in the eight studies that included only women with UFs may have led to an overestimation in MBL reduction with levonorgestrel IUD use.[30]

Two cohort studies and six non-comparative studies reported on levonorgestrel IUD expulsion rates in women with UFs. The two cohort studies demonstrated increased levonorgestrel IUD expulsion rates in women with UFs (11%) compared with those without UFs (0% and 3%), although statistical significance was either not assessed or not reached. Additionally, a significantly higher rate of levonorgestrel IUD expulsion in women with larger uterine volumes was reported in one of the cohort studies. This may also be potentially important, as uterine size has been previously used as a surrogate for fibroid size.[30] Expulsion rates observed in the other prospective non-comparative studies ranged from 0% to 20%.[30] Included study limitations were small samples sizes, a small number of studies assessing expulsion rates in women with UFs, and the fact that one of the cohort studies did not attempt to examine expulsion rates in those with and without UFs. The authors also noted that one of the cohort studies lacked a six-month follow-up, potentially underestimating expulsion rates (which normally occur in the months following insertion).[30] In addition, both this section (expulsion rates) and the previously noted section (uterine bleeding) observed only women using levonorgestrel IUD for therapeutic purposes and not for contraceptive use, which could have introduced some bias.[30]

The systematic review[30] was generally of high quality, but lacked the following AMSTAR criteria: did not list excluded studies, did not perform study selection or data extraction in duplicate, did not provide an explanation of potential publication bias, and contained no conflict of interest statement.[30] The

predominant limitations of the systematic review included the small sample sizes associated with the included studies, which could potentially introduce a high risk of bias; the risk of overestimation of MBL reduction with levonorgestrel IUD; and the underestimation of expulsion rates in women not assessed at a six-month follow-up. In addition, these trials assessed only levonorgestrel IUD for therapeutic use, thereby potentially reducing the generalizability to those using the device for contraception.

Summary

There are several classes of drugs used to manage UFs (GnRH agonists and levonorgestrel IUD) during the preoperative period; however, none of these have this specific indication. Two higher-quality systematic reviews were identified in women with UFs, one examining the effects of preoperatively administered GnRH agonists on operative times, intraoperative bleeding, and post-operative hemoglobin, and the other on levonorgestrel IUD expulsion rates. GnRH agonists were observed to reduce intraoperative bleeding and improve post-operative hemoglobin concentrations when compared with placebo. However, GnRH agonists did not have any effect on operative times. No increases in MBL and a decrease in MBL with continued use was observed upon levonorgestrel IUD use. In general, preoperative treatment with GnRH agonists appears to be an appropriate treatment for the reduction of intraoperative bleeding in women with UFs. The use of the levonorgestrel IUD did not increase MBL and decreased MBL with continued use; however, these results need to be interpreted with caution due to small sample size, the potential for overestimation of MBL reduction, and the potential for underestimation of expulsion rates.

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