CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ULIPRISTAL ACETATE (FIBRISTAL — ALLERGAN INC.)
Indication: Uterine fibroids

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

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

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

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Reasons for the Recommendation:

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

Of Note:

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

$25,000. Therefore, it is unclear whether six months of treatment with leuprolide acetate prior to hysterectomy is a more cost-effective option compared with four courses of ulipristal acetate. The committee also recognized that four courses of ulipristal acetate should have been compared with a wider range of treatment options (e.g., abdominal hysterectomy or embolization) in the cost-effectiveness analysis. However, additional economic analyses were limited due to the lack of comparative clinical information and, as such, the economic impact of the use of ulipristal acetate on the health care system remains uncertain.

Discussion Points:

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

Background:

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

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

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

Submission History:

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

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

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

Summary of CDEC Considerations:

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

Patient Input Information

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

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

Clinical Trials

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

The main limitation of the PEARL IV trial that may affect the internal validity of the results is the high attrition rate in the trial. More than 20% of the patients dropped out, mostly due to "subject request." Other patients who withdrew did so for a variety of reasons including lack of efficacy, pregnancy, and adverse events. Other limitations include the lack of a control group to the 5 mg ulipristal group, and the lack of data on the long-term safety and efficacy of ulipristal acetate beyond four courses of treatment.

Outcomes

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

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

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

Results

Efficacy

At the end of the four treatment courses, 48.7% of the patients (95 out of 195) in the 5 mg group were identified as achieving amenorrhea. Sensitivity analyses conducted with this population showed that when missing data were imputed as failures, the proportion of patients that achieved amenorrhea was 41.7% (95 out of 228); when missing data were assumed to be successes, the proportion of patients that achieved amenorrhea was 49.1% (112 out of 228). The pictorial blood-loss assessment chart showed a decrease from a mean of 300.2 at baseline to 139.7 after treatment course 4, 76.6% of patients (121 out of 158) achieved a 25% or more reduction in the fibroid size at the end of the follow-up, and patients experienced numerical improvements in their median UFS-QoL symptoms severity score during treatment. Patients tended to demonstrate fewer numerical improvements in the off-treatment period compared with the period immediately following the conclusion of a treatment course; however, the clinical significance of these findings is unclear due to the lack of minimal clinically important difference. No established minimal clinically important difference was available for the proportion of patients with amenorrhea, change in pictorial blood-loss assessment chart, change in UFS-QoL, change in pain score, or change in fibroid or uterine size.

Harms (Safety and Tolerability)

Most treatment emergent adverse events were reported during the first course of treatment, with 102 patients out of 230 (44.3%) reporting at least one adverse event in the 5 mg group. Subsequently, this percentage is recorded at 27.4%, 16.6%, and 23.9% for treatment courses 2, 3, and 4, respectively. Headaches were the most commonly reported adverse event, followed closely by hot flushes, which also decreased in incidence with subsequent treatment courses. Overall, 16 patients (7%) discontinued their treatment from the 5 mg group during the study due to adverse events. Serious adverse events were reported as five cases of menorrhagia, one case of bipolar disorder, one case of spontaneous myoma expulsion, one case of abdominal pain, and one case of back pain.

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

Cost and Cost-Effectiveness

Ulipristal acetate is available as a 5 mg tablet at the list price of $11.46. At the recommended dose of 5 mg daily for three months, the cost of a 90-day course of treatment is $1,031. While not specifically indicated for the treatment of signs and symptoms of uterine fibroids, leuprolide acetate may be used once monthly (3.75 mg injection) or once every three months (11.25 mg injection) for up to six months to manage this condition, at a cost of $1,071 to $1,078.

In response to a request from CADTH, the manufacturer submitted a cost-utility analysis based on a Markov state-transition model comparing four courses of ulipristal acetate (four courses of three months on treatment and two months off treatment) with one course of ulipristal acetate (three months on treatment, then two months off) followed by leuprolide acetate, over a 20 month time horizon. The manufacturer also considered an additional analysis comparing ulipristal acetate (four courses) with abdominal

hysterectomy (where leuprolide acetate was used six months for pre-surgical treatment). In the manufacturer's base-case analysis, the regimen of four courses of ulipristal acetate was dominant over a single course of treatment with ulipristal acetate followed by monthly injections of leuprolide acetate; namely, ulipristal acetate costs less ($4,606 versus $7,486) and is more effective (1.113 QALYs versus 1.109 QALYs). In the scenario analysis, abdominal hysterectomy cost more but was associated with greater QALYs than ulipristal acetate, resulting in an incremental cost-utility ratio of $3.9 million per QALY for abdominal hysterectomy, suggesting that abdominal hysterectomy is not cost-effective compared with ulipristal acetate.

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

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

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

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

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

CDEC Members:

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

October 18, 2017 Meeting

Regrets:

None

Conflicts of Interest:

None