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 22, 2017.

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ulipristal acetate should be reimbursed for the preoperative treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age; and for the intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery, with the duration of each treatment course being three months, if the following conditions are met:

Conditions for Reimbursement

Prescribing conditions:

- The patient is under the care of an obstetrician/gynecologist.
- Treatment should be limited to a maximum of four courses of therapy.
- Patients receiving ulipristal acetate should have their liver function tests monitored before, during, and after treatment.

Service Line: CADTH Drug Reimbursement Recommendation
Version: 1.0
Publication Date: July 2019
Report Length: 7 Pages

CADTH

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

CADTH

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 22, 2017.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ulipristal acetate should be reimbursed for the following indications:

1. Preoperative treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age.
2. Intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery, with the duration of each treatment course being three months.

Conditions for Reimbursement

Prescribing conditions:

- The patient is under the care of an obstetrician/gynecologist.
- Treatment should be limited to a maximum of four courses of therapy.
- Patients receiving ulipristal acetate should have their liver function tests monitored before, during, and after treatment.

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.
4. A safety review by Health Canada in January 2019 concluded that there may be an association between ulipristal acetate and serious liver injury. As a result, the Health Canada indication was altered: ulipristal acetate is now contraindicated in patients with a history of, or active, liver disease. Health Canada also restricted the intermittent use of ulipristal to women of child-bearing age who are not eligible for surgery.

Implementation Considerations

- CDEC noted that the drug plan costs for ulipristal acetate should still not exceed the drug plan costs for the manufacturer's identified comparator, leuprolide acetate, as specified in the original CDEC recommendation.
- Based on the November 2017 indication for ulipristal acetate, the CADTH Common Drug Review (CDR) reanalysis found six months of treatment with leuprolide acetate, followed by abdominal hysterectomy, to be more effective but costlier than four courses of ulipristal acetate, with an incremental cost per quality-adjusted life-year (QALY) gained of $25,158. This value of the incremental cost per QALY gained is within a range that is normally considered by CDEC to reflect cost-effective treatment options, which suggests that treatment with leuprolide acetate prior to hysterectomy is the optimal therapeutic choice. However, the manufacturer did not include any utility benefit from avoiding hysterectomy for women who wish to preserve their uterus. As this is an option that many patients would prefer compared with undergoing surgery (based on input from patient groups and the clinical expert consulted for this review), the inclusion of such a utility benefit would have decreased the cost-effectiveness of treatment with six months of leuprolide acetate prior to hysterectomy. When combined with uncertainty around the cost-

effectiveness estimate for the treatment with leuprolide acetate, failure to consider any potential utility benefits because of the avoidance of surgery increases the likelihood that the incremental cost per QALY gained of treatment with six months of leuprolide acetate prior to hysterectomy will exceed $25,000. Therefore, it is unclear whether six months of treatment with leuprolide acetate prior to hysterectomy is a more cost-effective option compared with four courses of ulipristal acetate. The committee also recognized that four courses of ulipristal acetate should have been compared with a wider range of treatment options (e.g., abdominal hysterectomy or embolization) in the cost-effectiveness analysis. However, additional economic analyses were limited because of the lack of comparative clinical information and, as such, the economic impact of the use of ulipristal acetate on the health care system remains uncertain.

Discussion Points

- The committee noted that no new efficacy evidence from clinical trials is available for ulipristal acetate since the last CDEC recommendation in November 2017. The committee also noted the lack of new economic evidence for the patient population described in the 2018 Health Canada indication for ulipristal acetate, specifically women who are not eligible for surgery.
- The committee noted that the definition of surgery ineligibility in the recommendation is not clear and could include women who are not eligible for surgery because of anemia, obesity, or other comorbidities that would make surgery unadvisable, and for women who wish to avoid surgery.

Background

Ulipristal acetate received an updated (December 2018) Health Canada–approved indication for the preoperative treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age, and for intermittent treatment of moderate-to-severe signs and symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery. The duration of each treatment course is three months. Ulipristal acetate is an orally active selective progesterone receptor modulator, given at 5 mg daily dose, and is contraindicated for patients with active or a history of liver disease.

The CDR participating drug plans submitted a request for advice to CADTH with respect to the 2017 CDEC recommendation for ulipristal acetate for the treatment of uterine fibroids, requesting advice regarding the following:

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

Submission History

In November 2017, CDEC recommended that ulipristal acetate be listed according to the Health Canada indication at the time of the recommendation (i.e., 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) if the following conditions are met:

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

View the full 2017 CDEC recommendation:
https://cadth.ca/sites/default/files/cdr/complete/SF0528_Fibristal_RFA_complete_Nov_22_17.pdf

Summary of Evidence Considered by CDEC Considerations

CDEC considered the following information prepared by CDR: an updated systematic review of randomized controlled trials and pivotal studies of ulipristal acetate, a summary of Health Canada's safety review, and a patient group's 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:

- Fibroids have a significant impact on patients' lives; the most prominent symptoms of pain and bleeding can lead to effects on a woman's social and family life, as well as affecting their career and work life.
- Patients are aware of liver issues described by Health Canada and have noted that lab testing to monitor liver function has not impacted them in a negative way.
- Aside from ulipristal acetate, there is no long-term medical therapy available that decreases the fibroid size, has tolerable side effects, and maintains fertility. Patients expressed a concern over losing access to ulipristal acetate, a drug they regard as a conservative treatment option that provides bleeding control, is easy to administer, avoids surgery whenever possible, and reduces pain and bulking (i.e., bloating, abdominal pressure). Ulipristal acetate is regarded as a 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; the subsequent treatment course would start when the second menses began. PEARL IV included European patients who were premenopausal and had an average-sized uterine fibroid (a 3 cm diameter and a 12 cm diameter diagnosed by ultrasound), with excessive menstrual bleeding (a pictorial blood loss assessment chart score of greater than 100), with no major comorbidities, and no history of prior hormonal treatment or immediate history of radiological or surgical interventions. Of the two ulipristal acetate treatment groups, it is the 5 mg group that reflects the Health Canada–approved recommended dose for ulipristal acetate and, as such, only descriptive results for the 5 mg treatment group are presented here.

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

Outcomes

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

- the percentage of patients who achieve amenorrhea at the end of each of the treatment courses and at the end of all of the treatment courses
- a change in the pictorial blood loss assessment chart score
- changes in quality of life and symptoms as measured through the *Uterine Fibroid Symptom & Health-Related Quality of Life Questionnaire (UFS-QoL)*, 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).

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 who achieved amenorrhea was 41.7% (95 out of 228); when missing data were assumed to be successes, the proportion of patients who 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 because of 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)

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 flashes, 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.

On March 15, 2018, Health Canada announced that a safety review of ulipristal acetate will be conducted as a result of Canadian and European reports of serious liver-related adverse events. Health Canada's review concluded that there may be a link between the use of ulipristal acetate and liver injury. Ulipristal acetate is now contraindicated for women who currently have or previously had liver disease. Women for whom the drug is to be prescribed are required to have liver function tests monitored before, during, and after treatment.

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 for 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: 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. This suggests 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 its 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 with other acceptable treatment options. For the full eligible population, four courses of ulipristal acetate should have been compared with a wider range of treatment options, including abdominal hysterectomy and embolization in the base case. Further, to capture the benefits of preserving the uterus, utility benefits associated with the preservation should have been included, as this value may differ depending on whether the preservation of the uterus was for the purposes of maintaining fertility or some other rationale.

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

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

Based on the reanalysis, CADTH suggests that intermittent treatment with ulipristal acetate (four courses) was both less effective and less costly than six months' treatment with leuprolide acetate followed by abdominal hysterectomy. The incremental cost per QALY gained for six months' treatment with leuprolide acetate followed by abdominal hysterectomy, compared with intermittent treatment with ulipristal acetate (four courses), was $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 a CADTH reanalysis that remains speculative.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

June 19, 2019 Meeting

Regrets

None.

Conflicts of Interest

None.