CDEC FINAL RECOMMENDATION

ULIPRISTAL ACETATE
(Fibristal — Actavis Specialty Pharmaceuticals)
Indication: Uterine Fibroids

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that ulipristal acetate be listed for the treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age, who are eligible for surgery, if the following conditions are met:

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

Reasons for the Recommendation:
1. In two double-blind randomized controlled trials (RCTs) ulipristal acetate was shown to be superior to placebo (PEARL I) and non-inferior to leuprolide acetate (PEARL II) for decreasing menstrual bleeding in patients with uterine fibroids. In addition, ulipristal acetate was associated with fewer adverse events than leuprolide acetate in PEARL II.

2. At the submitted price, ulipristal acetate ($1,031 per three-month course) is less costly than leuprolide acetate ($1,042 per three-month course).

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

Background:
Ulipristal acetate (ulipristal) is indicated for the treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery. Ulipristal is available as 5 mg tablets and the recommended starting dose is 5 mg once daily initiated during the first seven days of menses and taken continuously for three months.

Summary of CDEC Considerations

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

Patient Input Information

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

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

Clinical Trials

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

Outcomes

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

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

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

Results

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

Efficacy

- The proportion of patients who achieved a PBAC score of less than 75 was 91.5% with ulipristal and 18.8% with placebo in PEARL I and 90.3% with ulipristal and 89.1% with leuprolide in PEARL II.
- The risk difference for achieving a PBAC score of less than 75 was reported as follows:
  - Ulipristal versus placebo: 72.7% (95% CI, 55.1% to 83.2%) in PEARL I.
  - Ulipristal versus leuprolide: 1.2% (95% lower confidence limit, –9.3%) in the per-protocol (PP) analysis and 1.0% (95% lower confidence limit, –9.4%) in the intention-to-treat (ITT) analysis in PEARL II; therefore, ulipristal was non-inferior to leuprolide in both PP and ITT analyses.
- In PEARL I, there were statistically significant differences in both hemoglobin (mean difference 0.9 g/dL; 95% CI, 0.4 g/dL to 1.4 g/dL) and hematocrit (mean difference 2.6%; 95% CI, 1.0% to 4.1%) favouring ulipristal compared with placebo. In PEARL II, there were no statistically significant differences between ulipristal and leuprolide in hemoglobin, hematocrit, or ferritin.
- The proportion of patients whose hemoglobin values increased to more than 12 g/dL was 85.3% and 77.1% in the ulipristal and placebo groups (PEARL I) respectively, and 77.4% and 76.3% in the ulipristal and leuprolide groups (PEARL II) respectively.
- In PEARL I, there was a statistically significant reduction in total myoma volume favouring ulipristal compared with placebo (median difference –22.6%; 95% CI, –36.1% to –8.2%); however, the difference was not statistically significant when the data were log transformed.
- In PEARL II, there was no statistically significant difference between ulipristal and leuprolide on the log-transformed volume of the three largest myomas in the PP analysis; however, there was a statistically significantly difference favouring leuprolide in the ITT analysis (mean difference 0.10; 95% CI, 0.01 to 0.19).
- Bleeding was controlled more rapidly with ulipristal compared with leuprolide in PEARL II ($P < 0.001$).
- There were no statistically significant differences in quality of life or symptom control between treatments in either PEARL I or PEARL II, with the exception of an improvement in the Measurement of Discomfort Due to Uterine Fibroids Questionnaire with ulipristal versus placebo in PEARL I (mean difference –4.0; 95% CI, –6.0 to –1.0).

Harms (Safety and Tolerability)

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

- The proportion of patients who experienced at least one serious adverse event was reported as follows:
  - In PEARL I, 2.1% in the ulipristal group and 4.2% in the placebo group.
  - In PEARL II, 5.2% in the ulipristal group and 4.0% in the leuprolide group.
- No withdrawals due to adverse events occurred in PEARL I. In PEARL II, one (1.0%) was recorded in the ulipristal group and five (5.0%) were recorded in the leuprolide group.

Cost and Cost-Effectiveness

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

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

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

Other Discussion Points:

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

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

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

CDEC Members:

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

October 16, 2013 Meeting

Regrets:

None

Conflicts of Interest:

One CDEC member did not vote on the recommendation.

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

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

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