PRODUCT MONOGRAPH

PrFibristal™

ulipristal acetate

tablet, 5 mg

Selective Progesterone Receptor Modulator (SPRM)

Date of Preparation: June 19, 2013

Control No.: 156861

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PrFibristal™
ulipristal acetate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY OF PRODUCT INFORMATION

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<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
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<tr>
<td>Oral</td>
<td>Tablet, 5 mg</td>
<td>For a complete listing see Dosage Forms, Composition and Packaging section.</td>
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INDICATIONS AND CLINICAL USE

Fibristal (ulipristal acetate) is indicated for:

- Treatment of moderate to severe signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery. The duration of treatment is limited to 3 months.

Geriatrics (≥ 65 years of age): Safety and efficacy of Fibristal have not been established in women ≥ 65 years of age.

Pediatrics (< 18 years of age): Safety and efficacy of Fibristal have not been established in women < 18 years of age.

CONTRAINDICATIONS

- Fibristal is contraindicated in women who are hypersensitive to ulipristal acetate or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- Fibristal is contraindicated for use during pregnancy and in women who are breastfeeding.
- **Fibristal** is contraindicated in women with genital bleeding of unknown etiology or for reasons other than uterine fibroids.

- **Fibristal** is contraindicated in women with uterine, cervical, ovarian or breast cancer.

- Due to lack of long-term safety data, the duration of treatment should not be longer than 3 months of continuous use.

**WARNINGS AND PRECAUTIONS**

Ulipristal acetate should only be prescribed after careful diagnosis. Pregnancy should be precluded prior to treatment.

**Contraception**

Concomitant use of progestagen-only pills, a progestagen-releasing intrauterine device or combined oral contraceptive pills is not recommended. Although a majority of women taking a therapeutic dose of ulipristal acetate have anovulation, a non-hormonal contraceptive method is recommended during treatment.

**Hepatic Impairment**

Ulipristal acetate is not recommended in patients with mild, moderate, or severe hepatic impairment unless the patient is closely monitored.

**Renal Impairment**

Renal impairment is not expected to significantly alter the elimination of ulipristal acetate. In the absence of specific studies, ulipristal acetate is not recommended for patients with moderate and severe renal impairment unless the patient is closely monitored.

**Concomitant Treatments**

No dose adjustment is recommended in patients receiving **Fibristal** with mild CYP3A4 inhibitors. Co-administration of moderate or potent CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, erythromycin) and ulipristal acetate is not recommended.

When prescribing ulipristal acetate to patients receiving CYP3A4 inducers, plasma levels of ulipristal acetate may be reduced. Concomitant use of ulipristal acetate and potent enzyme inducers (e.g., rifampicin, carbamazepine, phenytoin, St John’s wort) is not recommended.

**Asthma Patients**

Use in women with severe asthma insufficiently controlled by oral glucocorticoids is not recommended.
Endometrial Changes

Ulipristal acetate has a specific pharmacodynamic action on the endometrium. Increase in thickness of the endometrium may occur. If the endometrial thickening persists beyond 3 months following the end of treatment and return of menstruations, this may need to be investigated as per usual clinical practice to exclude underlying conditions.

Changes in the histology of the endometrium may be observed in patients treated with ulipristal acetate. These changes are reversible after treatment cessation.

These histological changes are denoted as “Progesterone Receptor Modulator Associated Endometrial Changes” (PAEC) and should not be mistaken for endometrial hyperplasia. In absence of safety data for a period longer than 3 months or on repeat courses of treatment, the risk of adverse impact on the endometrium is unknown if treatment is continued; therefore, treatment duration should not exceed 3 months.

Bleeding Pattern

Patients should be informed that treatment with ulipristal acetate usually leads to a significant reduction in menstrual blood loss or amenorrhea within the first 10 days of treatment. Should the excessive bleeding persist, patients should notify their physician. Menstrual periods will generally return within 4 weeks after the end of the treatment course.

Special Populations

Pregnant Women: Use of Fibristal is contraindicated during an existing or suspected pregnancy. The extent of exposure in pregnancy during clinical trials is very limited.

Nursing Women: It is not known if ulipristal acetate is excreted in human milk. However, ulipristal acetate is detected in milk of lactating rats. Because many drugs are excreted in human milk, risk to the breast-fed child cannot be excluded. Breastfeeding while taking Fibristal is not recommended.

Pediatrics (< 18 years of age): Safety and efficacy of Fibristal have not been established in women < 18 years of age.

Geriatrics (≥ 65 years of age): Safety and efficacy of Fibristal have not been established in women ≥ 65 years of age.

Monitoring and Laboratory Tests

Pregnancy should be excluded before prescribing Fibristal. If pregnancy cannot be excluded on the basis of history and/or physical examination, pregnancy testing should be performed. If there is any doubt concerning the general health or pregnancy status of any woman after taking Fibristal, further investigation may be warranted.
ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse drug reactions (≥ 5%) in the clinical trials for women receiving Fibristal 5 mg were hot flash (13.0% overall) and headache (8.3% overall).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Fibristal was studied in a randomized, double-blind, placebo-controlled multicenter trial (Study 1) and in a randomized, double-blind, active comparator-controlled multicenter trial (Study 2). In these studies, a total of 393 (192 + 201) women in 5 mg and 10 mg ulipristal acetate groups, respectively, were included in the safety analysis. The mean age of women who received ulipristal acetate in Study 1 was 42 years and the body mass index (BMI) was 25.3. The racial demographics of those enrolled were 88% Caucasian and 12% Asian. The mean age of women who received ulipristal acetate in Study 2 was 40 years and the mean BMI was 25.5. The racial demographics of those enrolled were 85% Caucasian, 10% Black, 1% Asian, and 5% other.

Adverse drug reactions reported in at least 1% of subjects in any treatment group, in either study are shown in Table 1.
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<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reactions (MedDRA)</th>
<th>Study 1</th>
<th>Study 2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Ulipristal acetate 5 mg/day N = 95</td>
<td>Ulipristal acetate 10 mg/day N = 98</td>
<td>Placebo N = 48</td>
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<tr>
<td>Cardiac disorders</td>
<td>Sinus bradycardia</td>
<td>1 (1.1)</td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
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<td>Endocrine disorders</td>
<td>Hypeprolactinemia</td>
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<td></td>
<td>Hyperthyroidism</td>
<td>2 (2.1)</td>
<td>1 (1.0)</td>
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<td></td>
<td>Thyroid disorder</td>
<td>1 (1.1)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
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<td></td>
<td>Nausea</td>
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<td>2 (2.0)</td>
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<td></td>
<td>Constipation</td>
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<td>Abdominal pain upper</td>
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<td>Dyspepsia</td>
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<td>General disorders and administration site conditions</td>
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<td>Asthenia</td>
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<td>Irritability</td>
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<td></td>
<td>Edema</td>
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<td>Generalized edema</td>
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<td>Pyrexia</td>
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<td>Infections and infestations</td>
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<td>Vulvovaginal candidiasis</td>
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<td>Herpes virus infection</td>
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<td>Pharyngitis</td>
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<td>Investigations</td>
<td>Weight increased</td>
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<td></td>
<td>Gamma-glutamyltransferase increased</td>
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<td></td>
<td>Activated partial thromboplastin time prolonged</td>
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<td>Hypertriglyceridemia</td>
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<td></td>
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<td>Fluid retention</td>
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<td>Muscle spasms</td>
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<td>Back pain</td>
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<td>Pain in extremity</td>
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<td>Nervous system disorders</td>
<td>Headache</td>
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<td>3 (3.1)</td>
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<tr>
<td></td>
<td>Migraine</td>
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<td>Somnolence</td>
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<td></td>
<td>Dizziness</td>
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<td>Neoplasms benign, syndrome</td>
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<tr>
<td>System Organ Class (MedDRA)</td>
<td>Adverse Reactions</td>
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<td>Placebo N = 48</td>
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<tr>
<td>malignant and unspecified (incl cysts and polyps)</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
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<tr>
<td>Depression</td>
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<td>Affect lability</td>
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<td>Aggression</td>
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<td>Sleep disorder</td>
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<td>Reproductive system and breast disorders</td>
<td>Hot flush</td>
<td>1 (1.1)</td>
<td>1 (1.0)</td>
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<tr>
<td>Ovarian cyst</td>
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<td>1 (1.0)</td>
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<tr>
<td>Breast tenderness</td>
<td>3 (3.1)</td>
<td>3 (3.1)</td>
<td>3 (3.1)</td>
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<tr>
<td>Endometrial hypertrophy</td>
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<tr>
<td>Breast pain</td>
<td>2 (2.1)</td>
<td>2 (2.0)</td>
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<tr>
<td>Dysmenorrhea</td>
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<tr>
<td>Endometrial hyperplasia</td>
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<td>Genital hemorrhage</td>
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<td>Pelvic pain</td>
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<td>Menometrorrhagia</td>
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<td>Metrorrhagia</td>
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<tr>
<td>Uterine hemorrhage</td>
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<tr>
<td>Amenorrhea</td>
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<tr>
<td>Ovarian hyperfunction</td>
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<tr>
<td>Uterine disorder</td>
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<tr>
<td>Breast discomfort</td>
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<td>Vulvovaginal dryness</td>
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<tr>
<td>Breast swelling</td>
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<tr>
<td>Genital discharge</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>Epistaxis</td>
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<td>Skin and subcutaneous tissue</td>
<td>Night sweats</td>
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<tr>
<td>Acne</td>
<td>1 (1.1)</td>
<td>2 (2.0)</td>
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<tr>
<td>Hyperhidrosis</td>
<td>2 (2.0)</td>
<td>2 (2.0)</td>
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<tr>
<td>Seborrhea</td>
<td>1 (1.1)</td>
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<tr>
<td>Dry skin</td>
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<tr>
<td>Alopecia</td>
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<tr>
<td>Vascular disorders</td>
<td>Hyperemia</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Hypotension</td>
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</tbody>
</table>
Description of selected adverse reactions

Endometrial thickening

In 10-15% of patients, thickening of the endometrium (>16 mm by ultrasound or MRI at end of treatment) was observed with ulipristal acetate; this reverses when treatment is stopped and menstrual periods resume.

In addition, reversible changes to the endometrium are denoted PAEC and are different from endometrial hyperplasia. If hysterectomy or endometrial biopsy specimens are sent for histology, then the pathologist should be informed that the patient has taken ulipristal acetate.

Hot flush

Hot flushes were reported by 4 patients. In the placebo-controlled study, the rate of hot flushes was 1.7% for ulipristal acetate and 0% for placebo.

Headache

Mild or moderate severity headache was reported in 6.4% of patients.

Ovarian cyst

Functional ovarian cysts were observed during and after treatment in 1.5% of patients and in most of the cases spontaneously disappeared within a few weeks.

Uterine hemorrhage

Patients with heavy menstrual bleeding due to uterine fibroids are at risk of excessive bleeding, which may require surgical intervention. A few cases have been reported during ulipristal acetate treatment or within 2-3 months after ulipristal acetate treatment was stopped.

During clinical trials, the majority of adverse reactions were mild or moderate in severity. In Study 1, there were no subjects that discontinued the study due to adverse events. Additionally, in Study 2, Fibristal 5 mg demonstrated a lower rate of study discontinuation due to adverse events than the active comparator (1% for 5 mg ulipristal acetate vs. 5% for active comparator).

DRUG INTERACTIONS

Drug-Drug Interactions

Hormonal Contraceptives

Effect of Hormonal Contraceptives on Ulipristal Acetate

Ulipristal acetate has a steroid structure and acts as a selective progesterone receptor modulator with predominantly inhibitory effects on the progesterone receptor. Thus, hormonal contraceptives and progestogens are likely to reduce Fibristal efficacy.
Effect of Ulipristal Acetate on Hormonal Contraceptives

Ulipristal acetate may interfere with the action of hormonal contraceptive products (progestogen only, progestogen releasing devices or oral contraceptive pills) and progestogen administered for other reasons. Therefore concomitant administration of medicinal products containing progestogen is not recommended. Medicinal products containing progestogen should not be taken within 12 days after cessation of Fibristal treatment. Patients should be advised to use an alternative reliable barrier contraceptive method (such as a condom) while taking Fibristal.

CYP3A4 Inhibitors

Following administration of the moderate CYP3A4 inhibitor erythromycin propionate (500 mg twice daily for 9 days) to healthy female volunteers, C\text{max} and AUC of ulipristal acetate increased 1.2- and 2.9-fold, respectively; the C\text{max} of the active metabolite decreased (0.52-fold change), while the AUC of PGL4002, the mono-N-demethylated active metabolite of ulipristal acetate, increased 1.5-fold.

In the presence of the potent CYP3A4 inhibitor ketoconazole (400 mg once a day for 7 days), mean ulipristal acetate C\text{max} and AUC\text{0-inf} were increased by 1.96-fold and 5.86-fold, respectively. PGL4002 C\text{max} in the presence of ketoconazole was decreased by 0.53-fold while AUC\text{0-inf} was increased by 2.4-fold.

No dose adjustment is considered necessary for administration of ulipristal acetate to patients receiving concomitant mild CYP3A4 inhibitors. Co-administration of moderate or potent CYP3A4 inhibitors and ulipristal acetate is not recommended.

CYP3A4 Inducers

Patients receiving concomitant CYP3A4 inducers may have reduced plasma levels of ulipristal acetate. Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, St John’s wort) is not recommended.

P-gp Substrates

Following the co-administration of ulipristal acetate and fexofenadine (60 mg), mean fexofenadine AUC\text{and} C\text{max} were all minimally decreased in the presence of ulipristal acetate, with no effect on the time to maximum fexofenadine concentration. The co-administration of ulipristal acetate is not expected to result in a clinically relevant effect on the pharmacokinetics of P-gp substrates.

Oral Iron

The co-administration of ulipristal acetate and oral ferrous sulfate resulted in a 32% reduction in ulipristal acetate C\text{max} but only a 10% decrease in ulipristal acetate AUC with no effect on the time to achieve C\text{max} (T\text{max}) compared to ulipristal acetate administration without iron. A similar effect was seen for PGL4002, the mono-N-demethylated active metabolite of ulipristal acetate.
**Drug-Food Interactions**

**Fibristal** can be taken with or without food (see “Absorption” section under “Pharmacokinetics”).

**Drug-Herb Interactions**

Interactions with herbal products have not been established nevertheless St. John’s wort as a CYP3A4 inducer may decrease the plasma concentrations of ulipristal acetate, and may decrease its effectiveness (see section “Drug-Drug Interactions”).

**Drug-Laboratory Test Interactions**

No laboratory test interactions were observed during clinical evaluations.

**DOSAGE AND ADMINISTRATION**

The usual dose is one 5 mg tablet per day, for 3 months of continuous use. Instruct the patient to start taking **Fibristal** during the first 7 days of her menstrual period. The tablet should be swallowed with water and can be taken with or without food.

**Missed Dose**

If the patient misses a dose, she should take it as soon as it is remembered. However, if it is time for the next tablet, the patient should skip the missed tablet and take only a single tablet as usual.

**OVERDOSAGE**

Experience with ulipristal acetate overdose is limited.

Single doses up to 200 mg and daily doses of 50 mg for 10 consecutive days were administered to a limited number of subjects, and no severe or serious adverse reactions were reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

**ACTION AND CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Ulipristal acetate (which is the first, in a new class called selective progesterone receptor modulators [SPRM]) is an orally-active selective progesterone receptor modulator characterized by a tissue-specific, partial progesterone antagonist effect. Ulipristal acetate exerts a direct effect on the endometrium and exerts a direct action on fibroids reducing their size through inhibition of cell proliferation and induction of apoptosis.

A daily dose of ulipristal acetate inhibits ovulation and partially suppresses FSH levels but serum estradiol levels are maintained in the mid-follicular range in the majority of patients.
Electrocardiography

A double-blind ECG assessment study was conducted in 186 healthy female volunteers evaluating the potential effects of Fibristal on the QT/QTc interval using a 4-arm (Fibristal 10 mg [n=47], Fibristal 50 mg [n=47], placebo [n=47], moxifloxacin [n=45]), parallel group design. Fibristal did not significantly prolong or shorten the QTc interval at supratherapeutic oral doses of 10 mg/day or 50 mg/day for 8 days.

Pharmacokinetics

Absorption

Following single-dose oral administration of 5 mg, ulipristal acetate is rapidly absorbed, with a C\textsubscript{max} of 23.5 ± 14.2 ng/mL occurring approximately 1 hour after ingestion, and with an AUC\textsubscript{0-\infty} of 68.5 ± 33.0 ng·h/mL. Ulipristal acetate is rapidly transformed into PGL4002, the pharmacologically active mono-N-demethylated active metabolite with a C\textsubscript{max} of 9.0 ± 4.4 ng/mL also occurring approximately 1 hour after ingestion, and with an AUC\textsubscript{0-\infty} of 29.1 ± 12.9 ng·h/mL.

Administration of ulipristal acetate after a high-fat meal resulted in a slower rate of ulipristal acetate absorption as indicated by a 26 - 27% decrease in C\textsubscript{max} and a delay of about 1.5 hours in median T\textsubscript{max} for both ulipristal acetate and PGL4002. However, the extent of absorption was increased in the presence of food as evidenced by an increase in AUC\textsubscript{0-\infty} of 26% compared to that observed after ulipristal acetate administration in the fasted state. Because of the modest degree of these changes, ulipristal may be taken without regard to food.

The rate of absorption of ulipristal acetate is pH-dependent. Administration of ulipristal acetate together with the proton pump inhibitor esomeprazole (20 mg daily for 6 days) resulted in approximately 65% lower mean C\textsubscript{max}, a delayed t\textsubscript{max} (from a median of 0.75 hours to 1.0 hours) and 13% higher mean AUC (close to bioequivalence levels). Similar results were obtained for the active mono-N-demethylated metabolite. This kinetic effect of medicinal products that increase gastric pH is not expected to be of clinical relevance for daily administration of Fibristal tablets.

Distribution

Ulipristal acetate is highly bound (>98%) to plasma proteins, including albumin, alpha-l-acid glycoprotein, high density lipoprotein and low density lipoprotein.

Metabolism

Ulipristal acetate is metabolized to mono-N-demethylated (PGL4002) and di-N-demethylated (PGL4004) metabolites. In vitro data indicate that this is predominantly mediated by CYP3A4. The mono-demethylated metabolite is pharmacologically active.
**Excretion**

Due to the CYP-mediated metabolism, hepatic impairment is expected to alter the elimination of ulipristal acetate, resulting in increased exposure. The main route of elimination is through feces and less than 10% is excreted in the urine. The terminal half-life of ulipristal acetate in plasma following a single dose is estimated to be about 38 hours, with a mean oral clearance (CL/F) of about 100 L/h.

**Special Populations and Conditions**

**Pediatrics and Geriatrics:** No pharmacokinetic studies with ulipristal acetate have been performed in the pediatric or geriatric populations.

**Hepatic and Renal Insufficiency:** No pharmacokinetic studies with ulipristal acetate have been completed in women with impaired renal or hepatic function.

**STORAGE AND STABILITY**

Store at controlled room temperature (15 to 30° C).

Tablets packaged in blisters: Keep the blister cards inside the outer carton in order to protect from light.

Tablets packaged in bottles with desiccant: Keep tablets inside the bottle in order to protect from light.

**Keep out of reach of children.**

**SPECIAL HANDLING INSTRUCTIONS**

There are no special handling instructions.

**DOSAGE FORMS, COMPOSITION AND PACKAGING**

**Fibristal** (ulipristal acetate) tablet, 5 mg is supplied in two packaging options:

- Blister packages containing 7 or 15 tablets.
- Bottles containing 7, 30, or 90 tablets

The tablet is a white to off-white, round and biconvex tablet marked with “ES5” on one side.

The inactive ingredients are croscarmellose sodium, magnesium stearate, mannitol microcrystalline cellulose, and talc.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

**Proper Name:** ulipristal acetate

**Chemical name(s):** 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione;

19-Norpregna-4,9-diene-3,20-dione, 17-(acetoxy)-11-[4-(dimethylamino)phenyl]-,(11β)-

11β-[4-(dimethylamino)phenyl]-3,20-dioxo-19-norpregna-4,9-dien-17-yl acetate

**Molecular formula and molecular mass:** C_{30}H_{37}NO_{4}; 475.6

**Structural formula:**

![Structural formula image]

**Physiochemical properties:** Ulipristal acetate is a white to yellow crystalline powder. Micronized ulipristal acetate is freely soluble in methylene chloride, soluble in methanol, acetone and ethanol, and insoluble in water.

CLINICAL TRIALS

**Study Demographic and Trial Design**

The efficacy of ulipristal acetate 5 mg once daily was evaluated in two Phase 3 randomized, double-blind, 13 week studies recruiting subjects with heavy menstrual bleeding associated with uterine fibroids and at least one myoma measuring 3 cm or more in diameter. Both studies also evaluated a higher 10 mg daily dose of ulipristal acetate. This higher dose is investigational and not approved for use in Canada. Study 1 was double-blind placebo controlled and recruited subjects with fibroid related anemia at study entry. Study 2 contained the GnRH agonist active comparator/leuprolide 3.75 mg (not approved in Canada for the treatment of uterine fibroids) given once per month by intramuscular injection. In Study 2, a double-dummy method was used to maintain the blind.

In both studies menstrual blood loss was assessed using the Pictorial Bleeding Assessment Chart (PBAC). The PBAC was initially developed as a screening tool to discriminate between
menorrhagia and normal blood loss and has been extensively used as a tool to describe the reduction of menstrual blood loss in clinical trials. In this context, a PBAC score of 100 corresponds to approximately 80 mL of blood loss which is considered the threshold for heavy menstrual bleeding.

Study 1
This study was a multicenter, double-blind, placebo-controlled trial. Subjects were enrolled at 38 sites in six countries in Europe. Pre-menopausal women with symptomatic uterine myoma(s), excessive uterine bleeding (a PBAC >100 within the first 8 days of menses is considered to represent excessive menstrual blood loss) and anemia (hemoglobin [Hb] <10.2 g/dL) who were eligible for surgery (N=241) with a mean age of 42 years received a dose of 5 mg (n=95) or 10 mg (n=98) ulipristal acetate (Fibristal) or placebo (n=48). All subjects received 80 mg elemental iron (Fe^{2+}) orally once daily in addition to study drug or placebo. The mean BMI for the study subjects was 25.3 and ranged from 18.0 to 40.1.

The primary endpoints were the percentage of subjects with reduction in uterine bleeding defined as a PBAC score <75 at end-of-treatment visit (Week 13) and the change in total myoma volume assessed by magnetic resonance imaging (MRI) from screening to end-of-treatment visit (Week 13). Secondary endpoints were the following: change from baseline to Week 5, Week 9, and Week 13 visits in bleeding pattern recorded by subjects using the PBAC; change from baseline to Week 5, Week 9 and Week 13 visits in Hb, hematocrit (Hct) and ferritin; percentage of subjects in amenorrhea at Week 5, Week 9 and Week 13 visits; percentage of subjects in amenorrhea at Week 5, Week 9 and Week 13 visits; percentage of subjects with a volume reduction of ≥25% of the total myoma volume assessed by MRI at Week 13 visit; percentage of subjects with a reduction of ≥25% of uterine volume assessed by MRI at Week 13 visit; change from screening to Week 13 visit in uterine volume assessed by MRI; change from baseline to Week 5, Week 9, and Week 13 visits in global pain score (Short Form McGill Pain Questionnaire [SF-MPQ]); and change from baseline to Week 13 visit in symptoms related to uterine myomas (measurement of discomfort due to uterine fibroids questionnaire).

Study 2
This study was a multicenter, double-blind, active comparator-controlled comparison of the efficacy and safety of ulipristal acetate (Fibristal) to active comparator. Subjects were enrolled at 32 sites in seven countries in Europe. Pre-menopausal women with symptomatic uterine myoma(s) and excessive uterine bleeding who were eligible for surgery (N=301) with a mean age of 40 years were randomly allocated to receive Fibristal 5 mg (n=97) or 10 mg (n=103) or active comparator (n=101). Subjects were not required to be anemic to be enrolled in this study. The mean BMI for the study subjects was 25.5 and ranged from 18.1 to 39.8.

The primary endpoint was the percentage of subjects with reduction of uterine bleeding defined as a PBAC score <75 at end-of-treatment visit (Week 13 visit). The secondary endpoints were the following: change from baseline to Week 5, Week 9 and Week 13 visits in Hb, Hct, and ferritin; percentage of subjects in amenorrhea at Week 5, Week 9, and Week 13 visits; change from screening to Week 13 visit in the total volume of the three largest myomas assessed by ultrasound (US); change from screening to Week 13 visit in uterine volume assessed by US; change from baseline to Week 5, Week 9, and Week 13 visits in global pain score (SF-MPQ);
and change from baseline to Week 13 visit in Uterine Fibroid Symptom and health-related Quality of Life (UFS-QOL) score. The co-primary safety objectives were to show a superior side-effect profile for ulipristal acetate versus active comparator in terms of serum estradiol levels at Week 13 and the proportion of subjects with moderate-to-severe hot flashes during treatment. Secondary safety end points included hematologic and other laboratory assessments, including bone-turnover markers (urinary N-terminal propeptide of type I procollagen [P1NP], type I collagen C-telopeptide [CTX], and bone-specific alkaline phosphatase [BSAP] and deoxypyridinoline [DPD]).

The results in Table 2 reflect Fibristal 5 mg vs. placebo and Fibristal 5 mg vs. active comparator.

**Study Results**

**Table 2: Results of Primary and Selected Secondary Efficacy Assessments in Phase 3 Studies**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Ulipristal acetate 5 mg/day</td>
</tr>
<tr>
<td>Subjects whose menstrual bleeding became normal (PBAC &lt; 75) at Week 13</td>
<td>N = 48</td>
<td>N = 95</td>
</tr>
<tr>
<td>9 (18.8%)</td>
<td>86 (91.5%)</td>
<td>82 (89.1%)</td>
</tr>
<tr>
<td>Median change in myoma volume from baseline to Week 13</td>
<td>+3.0%</td>
<td>-21.2%</td>
</tr>
<tr>
<td>Menstrual bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PBAC at baseline</td>
<td>376</td>
<td>386</td>
</tr>
<tr>
<td>Median change at Week 13</td>
<td>-59</td>
<td>-329</td>
</tr>
<tr>
<td>Subjects in amenorrhea at Week 13</td>
<td>3 (6.3%)</td>
<td>69 (73.4%)</td>
</tr>
<tr>
<td>Median change in uterine volume from screening to Week 13</td>
<td>+5.88%</td>
<td>-12.1%</td>
</tr>
<tr>
<td>Hemoglobin change from baseline to Week 13 (g/dL) (adjusted mean)</td>
<td>+3.13</td>
<td>+4.05</td>
</tr>
<tr>
<td>Pain Assessment (SF-MPQ) change from baseline to Week 13 (median)</td>
<td>-2.5</td>
<td>-5.0</td>
</tr>
</tbody>
</table>

*In Study 1, change from baseline in total myoma and uterine volume was measured by MRI. In Study 2, change in the volume of the three largest myomas and uterine volume were measured by ultrasound. p-values (relative to placebo): 1 = <0.001, 2 = 0.002, 3 = 0.101.*
Study 1

Bleeding Symptoms

At Week 13, the percentage of subjects with PBAC score <75 was far greater with ulipristal acetate 5 mg (91.5%) than with placebo (18.8%) (p < 0.001). In addition, the decrease in mean PBAC at study Weeks 9 and 13 was statistically significant; p < 0.001) compared to placebo. Significantly more subjects were in amenorrhea with ulipristal acetate 5 mg compared to placebo at both Weeks 9 and 13 (p < 0.001). At Week 13, the percentage of subjects in amenorrhea was 6% with placebo, and 73% with ulipristal acetate.

Approximately 50% of the subjects in the ulipristal acetate 5 mg group became amenorrheic within the first 10 days of treatment as shown in Figure 1.

**Figure 1: Time to No Bleeding (Persistent Amenorrhea) (ITT Population)**

A return to normal bleeding (as defined by subsequent PBAC scores that were always <75) was achieved by Week 13 in the majority of subjects who were treated with ulipristal acetate 5 mg as shown in Figure 2.
Of the subjects who had not undergone hysterectomy or endometrial ablation, a total of 55 (72.4%) subjects from the ulipristal acetate 5 mg group returned to menstruation by Week 13. For those subjects, the mean time to return to menstruation after end of treatment was 19.9 days (median = 21.0 days).

**Hemoglobin and Hematocrit Values**

The mean increase in Hg at Week 13 with ulipristal acetate 5 mg was 4.1 g/dL compared with 3.1 g/dL for placebo (p<0.001). In addition, there was a mean increase of Hct at Week 13 of 10.0% with ulipristal acetate 5 mg versus 7.4% for placebo (p<0.001). Anemia was corrected by Week 13 in over 80% of subjects with anemia who received 5 mg ulipristal acetate. In addition, fewer subjects were anemic (defined as Hb ≤ 10.2 g/dL) at Week 13 with ulipristal acetate (4.0%) compared to placebo (11.4%).

**Fibroid and Uterine Volume**

A significantly greater proportion of subjects had a reduction in total fibroid volume ≥ 25% at Week 13 with ulipristal acetate 5 mg/day (41%) compared with placebo (18%) (p=0.014). Also, change in uterine volume from screening to Week 13 was statistically significant with a median % change of +5.9 cm³ with placebo and -12.1 cm³ with ulipristal acetate 5 mg (p=0.001).
Serum Estradiol

For the safety population (N=95), the mean serum estradiol value was 92.4 pg/mL in the ulipristal acetate 5 mg group at Week 13, which corresponds to mid-follicular phase levels for a pre-menopausal woman, and was 119.6 pg/mL in the placebo group.

Pain and Discomfort

There was a greater improvement in levels of pain as assessed by the Visual Analog Scale (VAS) from baseline to Week 9 between the ulipristal acetate 5 mg group (-31.23) and the placebo group (-18.42) (p=0.048).

A significantly greater improvement in discomfort measurements due to uterine fibroids, as determined using the Discomfort Due to Uterine Fibroids Questionnaire was seen for subjects in the ulipristal acetate 5 mg group versus placebo at Week 13 (median change from Baseline of -9.0 for ulipristal acetate vs. -6.0 for placebo; p=0.001).

Hot Flashes

The number and percentage of subjects reporting at least one episode of a moderate to severe hot flash during the treatment period was 2 (2.1%) (no hot flashes were reported in subjects in the placebo group).

Endometrial Changes

At Week 13, 10 subjects (10.5%) in the ulipristal acetate 5 mg group and one subject (2.1%) in the placebo group had endometrial thickness > 16 mm. At Week 13, endometrial-biopsy samples that were assessed centrally revealed no malignant or premalignant lesions or hyperplasia. However, non-physiological progesterone receptor modulator associated endometrial changes (PAEC) were observed more frequently in the ulipristal acetate 5 mg group than in the placebo group (41.6% and 7.9%, respectively). The results of the endometrial biopsies 6 months after the end of treatment showed that the non-physiological changes seen on treatment were generally reversible with only 1 subject (1.3%) in the ulipristal acetate 5 mg group and 1 subject (2.6%) in the placebo group with non-physiological changes at that timepoint.

Study 2

Bleeding Symptoms

Excessive bleeding was controlled more rapidly in subjects who received ulipristal acetate 5 mg than those who received active comparator, with the majority of ulipristal acetate 5 mg subject achieving persistent amenorrhea within 10 days, as shown in Figure 3.
Figure 3: Time to No Bleeding (Persistent Amenorrhea) (ITT Population)

A return to normal bleeding (as defined by subsequent PBAC scores that were <75 for the preceding 4 weeks) was achieved at Week 13 by 90% of the subjects receiving ulipristal acetate 5 mg and 89% of subjects receiving active comparator as shown in Figure 4.
Of the subjects who had not undergone hysterectomy or endometrial ablation, a total of 49 (63.6%) subjects from the ulipristal acetate 5 mg group returned to menstruation by Week 13, and a total of 22 (28.9%) of those treated with active comparator returned to menstruation by Week 13.

Following completion of treatment, the median time to return to menstruation was 25 days for subjects treated with ulipristal acetate 5 mg and 43 days for subjects treated with active comparator.

**Hemoglobin Values**

At Week 13, subjects treated with ulipristal acetate 5 mg had an adjusted mean change from baseline of +0.51 g/dL in Hg.
Fibroid and Uterine Volume

The volume of the three largest myomas was assessed by ultrasound at the end of treatment (Week 13) and at Week 26 (without further treatment) in subjects who did not have hysterectomy or myomectomy performed. For these subjects, the median percentage change from screening in the total volume of the three largest myomas in the ulipristal acetate 5 mg treatment group was -45.5% and -50.0% for Weeks 13 and 26, respectively (see Figure 5). This average decrease was generally maintained at Week 38 for subjects treated with ulipristal acetate 5 mg who did not undergo hysterectomy or myomectomy (median of -44.8%). Subjects who did not undergo hysterectomy or myomectomy and received active comparator had median values of -55.7% and -43.3% at Weeks 13 and 26 respectively. For these subjects, fibroids began to enlarge approximately 1 month after the last dose of active comparator acetate (median of -42.4% at Week 17) and continued to increase through week 38. However, fibroid volume reduction in subjects receiving ulipristal acetate appeared to be maintained in the majority of subjects for 6 months after the end of treatment.

Figure 5: Median Percentage Change from Screening to Weeks 13, 17, 26, and 38 in the Volume of the Three Largest Myomas in Subjects who did not have Surgery before Week 38

Serum Estradiol

For the safety population (N=97), the median serum estradiol value was 64.0 pg/mL in the ulipristal acetate 5 mg group and 60.5 pg/mL in the group receiving 10 mg of ulipristal acetate at Week 13, but decreased to postmenopausal levels in the active comparator group (25.0 pg/mL) (p<0.001 for each ulipristal group vs. active comparator). The number, and percentage, of
subjects reporting episodes of moderate or severe hot flashes during the treatment period was 11 (11.3%) for subjects treated with ulipristal acetate 5 mg, and 40 (39.6%) for subjects treated with active comparator.

Pain and Discomfort

The median change from baseline to Week 13 for responses to the SF-MPQ and VAS in subjects treated with ulipristal acetate 5 mg were -5.0 and -31.0, respectively. In addition, subjects in the 5 mg ulipristal acetate treatment group showed an improvement (-28.2) on average for the symptom severity score and an improvement (20.3) on average for the quality of life total score at Week 13 compared to baseline.

Endometrial Changes

At Week 13, the histologic specimens from subjects in the ulipristal acetate 5 mg group were all given a diagnosis of benign endometrium except for one who had a diagnosis of simple, non-atypical hyperplasia. Non-physiological endometrial changes at Week 13 were observed in 77.3% of the subjects in the ulipristal acetate 5 mg group, 79.6% of the subjects in the ulipristal acetate 10 mg group, and in 35.6% of subjects in the active comparator group. The results of the endometrial biopsies 6 months after the end of treatment showed that the non-physiological changes seen on treatment were generally reversible with only three subjects (3.9%) in the ulipristal acetate 5 mg group with non-physiological endometrial changes at that timepoint.

Bone Resorption

Due to the short duration of the clinical study, meaningful changes in bone markers were not expected. However, subjects treated with active comparator showed a significantly larger increase in median levels from baseline to Week 13 of type I CTX (101.5 mcg/mmol to 258.0 mcg/mmol) compared to subjects treated with ulipristal acetate (117.0 mcg/mmol to 175.0 mcg/mmol) (p>0.001).

DETAILED PHARMACOLOGY

Ulipristal acetate is an orally-active selective progesterone receptor modulator characterized by a tissue-specific partial progesterone antagonist effect.

Endometrium

Ulipristal acetate exerts a direct effect on the endometrium. When daily administration of a 5 mg dose is commenced during a menstrual cycle most subjects (including subjects with myoma) will complete their first menstruation but will not menstruate again until after treatment cessation. Upon ulipristal acetate treatment cessation, menstrual cycles generally resume within 4 weeks.

The direct action on the endometrium results in class-specific benign changes in histology termed, PAEC. Typically, the histological appearance is an inactive and weakly proliferating epithelium associated with asymmetry of stromal and epithelial growth resulting in prominent cystically dilated glands with admixed estrogen (mitotic) and progestin (secretory) epithelial effects. Such a pattern has been observed in approximately 60% of subjects treated with
Fibri-stal for 3 months. These changes are reversible after treatment cessation. These changes should not be confused with endometrial hyperplasia.

About 5% of patients of reproductive age experiencing heavy menstrual bleeding have an endometrial thickness of greater than 16 mm. Endometrial thickening >16 mm was observed in approximately 11% of subjects treated with Fibristal. This thickening disappears after treatment is withdrawn and menstruation occurs. If endometrial thickness persists beyond the 3 months following the end of treatment and return of menstruation then this may need to be investigated as per usual clinical practice to exclude underlying conditions.

Fibroids

Ulipristal acetate exerts a direct action on fibroids reducing their size through inhibition of cell proliferation and induction of apoptosis.

Pituitary

A daily dose of ulipristal acetate 5 mg inhibits ovulation in the majority of subjects as indicated by progesterone levels maintained at around 0.3 ng/mL.

A daily dose of ulipristal acetate 5 mg partially suppresses FSH levels but serum estradiol levels are maintained in the mid-follicular range in the majority of subjects and are similar to levels in subjects who received placebo.

Ulipristal acetate does not affect serum levels of TSH, ACTH or prolactin during 3 months of treatment.

TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

Most findings in general toxicity studies were related to the action of ulipristal acetate on progesterone receptors, with antiprogestosterone activity observed at exposures similar to therapeutic levels. In a 39 week study in cynomolgus monkeys, histological changes resembling PAEC were noted at low doses.

Due to its mechanism of action, ulipristal acetate has an embryolethal effect in rats, rabbits (at repeated doses above 1 mg/kg), guinea pigs and in monkeys. The safety for a human embryo is unknown. At doses which were low enough to maintain gestation in the animal species, no teratogenic potential was observed.

Reproduction studies performed in rats at doses giving exposure in the same range as the human dose have revealed no evidence of impaired fertility due to ulipristal acetate in treated animals or the offspring of treated females.

Administration of ulipristal acetate at dose levels up to 10 mg/kg/day for at least 99 weeks in female rats and 100 weeks in male rats resulted in significant reductions in bodyweight gain but
no evidence of an increase in tumors. In addition, Transgenic Hemizygous CBByB6F1-
Tg(HRAS)2Jic mice were dosed with ulipristal acetate at 0, 15, 45, or 130 mg/kg/day for
26 weeks. There was no evidence of any test article-induced carcinogenicity. Based on these
data, ulipristal acetate is not considered to be carcinogenic up to the highest doses tested.
PART III: CONSUMER INFORMATION

PR Fibristal™ ulipristal acetate

This leaflet is part III of a three-part "Product Monograph" published when Fibristal was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Fibristal. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Fibristal is used for the treatment of signs and symptoms of uterine fibroids in adult women of reproductive age who are eligible for surgery. The duration of treatment is limited to 3 months.

What it does:
Fibristal helps to reduce bleeding, reduce the size of uterine fibroids and improve other symptoms associated with uterine fibroids.

Fibristal is thought to work by selectively modifying the activity of progesterone, a naturally occurring hormone in the body.

When it should not be used:
Do not use Fibristal if you:
- Are allergic (hypersensitive) to ulipristal acetate or any of the other ingredients of Fibristal
- Are pregnant
- Are breastfeeding
- Have vaginal bleeding not caused by uterine fibroids
- Have uterine, cervical, ovarian or breast cancer
- Have already taken Fibristal for a period of three months

What the medicinal ingredient is:
Ulipristal acetate

What the nonmedicinal ingredients are:
Crocarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, and talc.

What dosage forms it comes in:
Fibristal is supplied as a tablet containing 5 mg of ulipristal acetate. These tablets are white to off-white, round and biconvex.

WARNINGS AND PRECAUTIONS

BEFORE you use Fibristal talk to your doctor or pharmacist if:
- You have liver or kidney disease
- You suffer from severe asthma
- You are pregnant or suspect to be pregnant
- You are taking a hormonal contraceptive. A non-hormonal contraceptive (such as condoms) is recommended while taking Fibristal during treatment.

Treatment with Fibristal usually leads to a significant reduction or may even stop the bleeding of your periods within the first days of treatment. However, if you continue to experience excessive bleeding, tell your doctor. Your period should generally return within 4 weeks after treatment with Fibristal is stopped.

The lining of the uterus may thicken or change as a result of taking Fibristal. These changes return to normal after treatment stops and your periods restart.

Fibristal should not be taken by children under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking any of the medicines listed below, as these medicines can affect Fibristal or be affected by Fibristal:
- Phenytoin, phenobarbital, carbamazepine (drugs to treat epilepsy)
- Ritonavir (drug to treat HIV infections)
- Rifampicin, telithromycin, clarithromycin, erythromycin (antibiotics)
- Ketoconazole (except shampoo), itraconazole (drugs to treat fungal infections)
- St John’s Wort (a herbal treatment for depression)
- Nefazodone (drug to treat depression)

Fibristal is likely to make some hormonal contraceptives less effective. In addition hormonal contraceptives and progestogens (e.g., norethindrone or levonorgestrel) are also likely to make Fibristal less effective. Therefore hormonal contraceptives are not recommended and you should use an alternative reliable barrier contraceptive method such as condoms during Fibristal treatment.

PROPER USE OF THIS MEDICATION

Usual dose:
The usual dose for women is one 5 mg tablet per day for 3 months.
You should start taking **Fibristal** during the first 7 days of your menstrual period. The tablet should be swallowed with water and may be taken with or without food. Always take **Fibristal** exactly as your doctor has told you. Never exceed the prescribed dose.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

If you miss a dose, take it as soon as you remember. However, if it is time for your next tablet, skip the missed tablet and take only a single tablet as usual. Do not take a double dose to make up for a forgotten tablet.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

**Fibristal** can have side effects, like all medicines, but not everybody gets them. For further information about any of these side effects, ask a doctor or pharmacist. If you experience any symptom that bothers you or does not go away, contact your doctor or seek medical attention as soon as possible.

In clinical studies, the most common side effects related to taking **Fibristal** were hot flash and headache.

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist</th>
<th>Stop taking drug and call your doctor or pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only if severe</td>
<td>In all cases</td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Hot flash</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal uterine bleeding</td>
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</tr>
<tr>
<td>Sac of fluid within the ovaries (ovarian cyst)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Worsening of uterine bleeding</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>New uterine fibroids</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

This is not a complete list of side effects. For any unexpected effects while taking **Fibristal**, contact your doctor or pharmacist.

**HOW TO STORE IT**

This package is sealed for your protection. Do not use if torn or broken.

Store at controlled room temperature (15 to 30°C).

Blisters: Keep the blister cards inside the outer carton in order to protect from light.

Bottles: Keep tablets inside the bottle in order to protect from light.

Keep **Fibristal** out of reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

**NOTE:** Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting the importer, Actavis Specialty Pharmaceuticals Co., at 1-855-892-8766

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