

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-474

OFFICE DIRECTOR MEMO



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: August 13, 2010

TO: NDA 022474
ella (ulipristal acetate) tablet, 30 mg, for oral use
Laboratoire HRA Pharma

FROM: Julie Beitz, M.D.
Director, Office of Drug Evaluation III

RE: Approval Action for NDA 022474

The **ella** tablet contains 30 mg of a single active steroid ingredient, ulipristal acetate, a synthetic progesterone agonist/antagonist and new molecular entity. The product is indicated for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. It is not intended for routine use as a contraceptive. Ulipristal acetate will be supplied as a single 30 mg tablet to be taken orally as soon as possible, within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure. This memorandum documents my concurrence with the Division of Reproductive and Urologic Product's (DRUP's) approval recommendation for ulipristal acetate for occasional use as an emergency contraceptive. Product labeling will contraindicate its use in women with known or suspected pregnancy, and will warn that pregnancy should be excluded before using ulipristal acetate. The product will be available by prescription only. Discussions regarding the product labeling, patient package insert¹, and postmarketing study requirements and commitments have satisfactorily concluded, and there are no manufacturing or inspectional issues that would preclude product approval.

Regulatory History

NDA 022474, submitted on October 14, 2009 and received on October 15, 2009, was granted a standard review. This application was presented before the Reproductive Health Drugs Advisory Committee on June 17, 2010. Committee members voted unanimously (11-0) that the applicant had provided sufficient information to conclude 1)

¹ Patient package inserts are required to be distributed for oral contraceptive products in accordance with 21 CFR 310.501 to ensure that women are fully informed of the benefits and risks involved in their use. The patient package insert is required to be placed in or accompany each package dispensed to the patient.

that ulipristal acetate reduces the likelihood of pregnancy when taken within 120 hours after unprotected intercourse or a known or suspected contraceptive failure, and 2) that the safety profile for ulipristal acetate is acceptable for the proposed indication. Committee members also voted unanimously that there was no need for measures beyond product labeling and healthcare provider education to address potential off-label use of ulipristal acetate. Committee members advised that product labeling 1) not require mandatory pregnancy testing prior to prescribing ulipristal acetate since pregnancy testing would likely be done in practice, and 2) recommend against use of the product by lactating women since data were not yet available regarding the possible exposure to ulipristal acetate to infants fed breast milk.

Clinical Pharmacology

Ulipristal acetate is a selective progesterone receptor modulator with antagonistic and partial agonistic effects. The product exerts its effects by binding to progesterone receptors in various tissues, such as the ovary and endometrium. The pharmacodynamics of ulipristal acetate depend on the timing of administration in the menstrual cycle. Administration in the mid-follicular phase causes inhibition of folliculogenesis and reduction of estradiol concentrations, whereas administration at the time of the luteinizing hormone peak delays follicular rupture by 5-9 days. Dosing in the early luteal phase does not significantly delay endometrial maturation but decreases endometrial thickness. There have been no clinical trials in women that assess the effect of ulipristal acetate on an existing pregnancy.

Following a single oral dose of ulipristal acetate 30 mg in 20 women under fasting conditions, maximum plasma concentrations of ulipristal acetate and the active metabolite, monodemethyl-ulipristal acetate, were reached at 0.9 and 1 hour, respectively. *In vitro* data indicate that the metabolism of ulipristal acetate is predominantly mediated by CYP3A4. The terminal half-life of ulipristal acetate in plasma following a single 30 mg dose is estimated to be 32.4 ± 6.3 hours.

Administration of ulipristal acetate together with a high-fat breakfast resulted in an approximately 40-45% lower mean C_{max} , a delayed t_{max} (from a median of 0.75 to 3 hours), and a 20-25% higher mean $AUC_{0-\infty}$ of both ulipristal acetate and monodemethyl-ulipristal acetate compared with administration in the fasting state. These differences are not expected to impair the efficacy or safety of ulipristal acetate to a clinically significant extent; therefore, ulipristal acetate can be taken with or without food.

In vitro studies have demonstrated that ulipristal acetate does not induce or inhibit the activity of CYP450 enzymes. However, since ulipristal acetate is primarily metabolized by CYP3A4, co-administration with CYP3A4 inhibitors may increase plasma concentrations of ulipristal acetate. Conversely, co-administration of CYP3A4 inducers may decrease plasma concentrations of ulipristal acetate and may decrease its effectiveness. The applicant has agreed to study the *in vivo* pharmacokinetic profile of ulipristal acetate in the presence of a CYP3A4 inducer post-approval.

No clinical trials have been conducted to evaluate the effect of hepatic or renal disease on the disposition of ulipristal acetate.

Non-Clinical Findings

Single oral doses of ulipristal acetate prevented ovulation in 50% of rats at 2 times the human exposure based on body surface area (mg/m^2). Single doses of ulipristal acetate given on post-coital days 4 or 5 prevented pregnancy in 80-100% of rats, and in 50% of rabbits when given on post-coital days 5 or 6 at drug exposures 4 and 12 times the human exposure based on body surface area. Lower doses administered for 4 days to rats and rabbits were also effective at preventing ovulation and pregnancy.

Ulipristal acetate was administered repeatedly to pregnant rats and rabbits during the period of organogenesis. Embryofetal loss was noted in all pregnant rats and in half of the pregnant rabbits following 12 and 13 days of dosing at drug exposures 1/3 and 1/2 the human exposure, respectively, based on body surface area. There were no malformations of the surviving fetuses in these studies. Adverse effects were not observed in the offspring of pregnant rats administered ulipristal acetate during the period of organogenesis through lactation at drug exposures 1/24 the human exposure based on AUC. Administration of ulipristal acetate to pregnant monkeys for four days during the first trimester caused pregnancy termination in 2/5 animals at drug exposures 3 times the human exposure based on body surface area.

In non-clinical studies, the potential for pregnancy termination by a single dose of ulipristal acetate was not assessed, and no study evaluated the effects of administration during the period immediately following implantation.

Carcinogenicity studies with ulipristal acetate have not been conducted.

Ulipristal acetate was not genotoxic in the Ames assay, *in vitro* mammalian assays utilizing mouse lymphoma cells and human peripheral blood lymphocytes, and in an *in vivo* micronucleus assay in mice.

Efficacy

The effects of ulipristal acetate 30 mg on pregnancy prevention were demonstrated in two multicenter clinical trials in women requesting emergency contraception. Women in both trials were required to have a negative pregnancy test prior to receiving emergency contraception to minimize potential confounding of the treatment effect by a pre-existing pregnancy. The primary analysis of efficacy was performed on the subgroup of enrolled women less than 36 years of age who had a known pregnancy status after taking study medication.

One trial² was an open-label trial which enrolled a total of 1533 healthy US women in Planned Parenthood family planning clinics (aged 18-50 years; mean 24 years). The body mass index or BMI of these women ranged from 16-61 kg/m^2 (median of 25 kg/m^2). The number of pregnancies expected without ulipristal acetate use was calculated based on the timing of intercourse with respect to each woman's menstrual cycle. For the efficacy population (n=1242), ulipristal acetate significantly reduced the pregnancy rate

² Fine PM, Mathe H, Ginde S et al. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. *Obstet Gynecol* 115:257-63, 2010.

from an expected 5.5% to an observed 2.2% (95% CI: 1.5, 3.2) when taken 48 to 120 hours after unprotected intercourse.

The second trial,³ conducted in family planning clinics in the US, UK, and Ireland, randomized 2221 women (aged 16-55 years; mean 25 years) to either a single dose of ulipristal acetate 30 mg or levonorgestrel 1.5 mg. Approximately 4% of subjects were under 18 years of age (44 subjects on ulipristal acetate and 49 on levonorgestrel). The median BMI of subjects ranged from 15-70 kg/m² (median of 25 kg/m²).

Both products significantly reduced the pregnancy rate when taken 0-72 hours after unprotected intercourse by women aged 16-35 years. For the 844 users of ulipristal acetate, the observed pregnancy rate was 1.9% (95% CI: 1.1, 3.1) instead of the expected 5.6%; for the 852 users of levonorgestrel, the observed pregnancy rate was 2.7% (95% CI: 1.8, 4.1) instead of the expected 5.5%. Among women who received treatment between 72 and 120 hours after unprotected intercourse, there were three pregnancies, all among levonorgestrel users.

Pooled efficacy analyses. Data from the two trials were pooled for selected analyses. A time trend analysis of efficacy for the five 24-hour intervals from 0-120 hours between unprotected intercourse and treatment was conducted. There were no significant differences in the observed pregnancy rates across the five time intervals.

For the subgroup of ulipristal acetate-treated women with a BMI > 30 kg/m² in the pooled trials, the observed pregnancy rate was 3.1% (95% CI: 1.7, 5.7) which was not significantly reduced compared to the expected pregnancy rate of 4.5% in the absence of emergency contraception taken within 120 hours after unprotected intercourse. In the comparative trial, for the subgroup of levonorgestrel-treated women with a BMI > 30 kg/m², the observed pregnancy rate was 7.4% (95% CI: 3.9, 13.4) compared to the expected pregnancy rate of 4.4% in the absence of emergency contraception taken within 72 hours after unprotected intercourse.

Safety

The clinical safety database for ulipristal acetate included 4,771 women, 2,764 of whom received the to-be-marketed tablet formulation. The most common adverse reactions reported in women receiving a single dose of ulipristal acetate 30 mg in clinical trials were: headache, nausea, abdominal pain, dysmenorrhea, fatigue and dizziness. This profile of adverse reactions is similar to that of marketed levonorgestrel emergency contraceptive products.

Use in pregnancy. Use of ulipristal acetate is contraindicated during an existing or suspected pregnancy. The pregnancy risk category for ulipristal acetate will be designated as category X. There are no adequate and well-controlled clinical trials of ulipristal acetate in pregnant women.

³ Glasier AF, Cameron ST, Fine PM et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. *Lancet* 375:555-62, 2010

Among 113 pregnancies that occurred in women taking ulipristal acetate for emergency contraception (92 reported in clinical trials and 21 reported following ex-US marketing approval in 2009), there were 7 live births and 14 pregnancies are ongoing. One infant had optic nerve hypoplasia and developmental delay, five infants were reported as normal, and the outcome of one birth is unknown. It is not known whether the single case of optic nerve hypoplasia and developmental delay is related to the use of ulipristal acetate. In non-clinical studies, no malformations were reported in any offspring of treated rats, rabbits, and monkeys. Thus, the risks to a fetus when ulipristal acetate is administered to a pregnant woman are unknown. If ulipristal acetate is inadvertently used during pregnancy, the woman should be apprised of the potential hazard to the fetus.

Maternal outcomes for the reported pregnancies included 62 elective terminations (60 in clinical trials and 2 in postmarketing experience), and 16 spontaneous abortions (15 in clinical trials and 1 in postmarketing experience). The rate of spontaneous abortion among ulipristal acetate users who became pregnant was similar to the background rate of spontaneous abortion (15-20%) and to the spontaneous abortion rate noted among levonorgestrel users who became pregnant in the comparative trial (13%).

Use in nursing mothers. It is not known if ulipristal acetate is excreted in human milk. However, ulipristal acetate is detected in milk of lactating rats. Lactating women were excluded from clinical trials of ulipristal acetate; thus, the risk to the breastfed child cannot be excluded. Ulipristal acetate is not recommended for use by breastfeeding women. The applicant will be required to study the effects of ulipristal acetate on breastfed infants post-approval.

Labeled warnings. Labeling for ulipristal acetate will carry several warnings. First, ulipristal acetate is not indicated for termination of an existing pregnancy. Pregnancy should be excluded before ulipristal acetate is prescribed. If pregnancy cannot be excluded on the basis of the woman's history and/or physical examination, then pregnancy testing should be performed.

The possibility of ectopic pregnancy should be excluded in women who become pregnant or complain of lower abdominal pain after taking ulipristal acetate. A follow-up physical or pelvic examination is recommended if there is any doubt concerning the general health or pregnancy status of any woman taking the product.

Labeling will warn against the use of ulipristal acetate as a regular method of contraception and against repeated use within the same menstrual cycle. The safety and efficacy of repeat use within the same menstrual cycle has not been evaluated. There were 88 women who were repeat enrollees in clinical trials of ulipristal acetate, including 9 women who enrolled three times. These women did not experience adverse events more frequently than women who enrolled only once.

Labeling will also warn that use of ulipristal acetate may reduce the contraceptive action of regular hormonal contraceptives due to its high affinity binding to the progesterone receptor. Thus, after use of ulipristal acetate, use of a reliable barrier method of contraception is recommended with subsequent acts of intercourse that occur in that same menstrual cycle.

After taking ulipristal acetate, menses may occur earlier or later than expected by a few days. Menstrual cycle length was increased by a mean of 2.5 days but returned to normal in the subsequent cycle. As many as 7% of women reported menses occurring more than 7 days earlier than expected, and 19% reported a delay in menses of more than 7 days. If the onset of expected menses is delayed beyond 1 week, pregnancy should be ruled out.

Lastly, labeling will warn that ulipristal acetate does not protect against HIV infection or other sexually transmitted infections.

A patient package insert will inform women of the risks associated with the use of ulipristal acetate.

Pediatric Considerations

Pediatric Use. The safety and efficacy of ulipristal acetate have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents less than 18 years and for users 18 years and older. Use of ulipristal acetate before menarche is not indicated.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because they are not at risk of becoming pregnant, and use of this product before menarche is not indicated. The applicant has fulfilled the pediatric study requirement for post-menarcheal pediatric patients by extrapolation of adult data.

Postmarketing Requirements under 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify any unexpected serious risks of adverse maternal, fetal or neonatal outcomes following exposure to ulipristal acetate during pregnancy, or adverse events associated with the use of ulipristal acetate by adolescents, particularly with respect to alterations in the menstrual cycle.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that the applicant is required to conduct the following:

- 1) a prospective observational pregnancy outcome study to include fetal and neonatal outcomes and maternal pregnancy complications following a pregnancy exposed to ulipristal acetate (e.g., in case of inadvertent administration to a woman with an unrecognized pregnancy, or in case of emergency contraceptive failure). This study may be conducted by adding a US component to the applicant's planned European pregnancy outcome study.
- 2) a case-control study of pregnancy loss complications. This study will be conducted as an expansion of the pregnancy outcome study (described above), if a signal of concern regarding pregnancy complications is found in that study.
- 3) an observational study in adolescents, with particular focus on alterations to the menstrual cycle after use of ulipristal acetate. This study may be conducted by adding a US component to the applicant's planned UK/Sweden study of use in adolescents. The study should enroll at least 50 subjects (completers) under the age of 16 over the full study (these do not necessarily have to be US subjects).

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess an unexpected serious risk of drug transfer from mother to child in lactating women.

Therefore, based on appropriate scientific data, FDA has determined that the applicant is required to conduct a pharmacokinetic trial in lactating women, with evaluation of the rate and extent of excretion of ulipristal acetate and its active metabolite into breast milk. The applicant's planned lactation trial to be conducted in Chile appears likely to fulfill this requirement.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), have concluded that the tradename "ella" is acceptable. The product has been marketed in Europe under the tradename "ellaOne" since October 2009.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22474

ORIG-1

LABORATOIRE
HRA PHARMA

Ella , Ulipristal Acetate

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/s/

JULIE G BEITZ
08/13/2010