

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-474

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 13, 2010
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 022474
Applicant Name	Laboratoire HRA Pharma
Date of Submission	October 15, 2009
PDUFA Goal Date	August 15, 2010
Proprietary Name	ella
Established (USAN) Name	Ulipristal acetate
Dosage Forms/Strengths	30 mg tablet
Proposed Indication	Emergency contraceptive for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure
Proposed Regimen	One tablet orally as soon as possible, within 120 hours (5 days) after unprotected intercourse
Action	<i>Approve (see Section 13.1)</i>

Material Reviewed/Consulted	Names of Discipline Reviewers
OND Action Package, including:	
Medical Officer Review	Ronald Orleans MD (primary Clinical Reviewer)
Statistical Review	Kate Dwyer PhD/Mahboob Sobhan PhD
Pharmacology Toxicology Review	Jeffrey Bray PhD/Alexander Jordan PhD
CMC Review	Bogdan Kurtyka PhD/Moo-Jhong Rhee PhD
Microbiology Review	Not required
Clinical Pharmacology Review	Hyunjin Kim PharmD/Myong-Jin Kim PharmD
DDMAC	Janice Maniwang PharmD/Carrie Newcomer PharmD
DSI	Roy Blay PhD/Tejashri Purohit-Sheth MD
CDTL Review	Lisa Soule MD (also Clinical Team Leader)
OSE/DMEPA	Walter Fava RPh/Carlos Mena Grillasca RPh/Denise Toyer PharmD
OSE/DRISK	Melissa Hulett MSBA, RN/Mary Willy PhD

OND=Office of New Drugs

CMC=Chemistry, Manufacturing and Controls

DDMAC=Division of Drug Marketing, Advertising, and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Errors Prevention and Analysis

DSI=Division of Scientific Investigations

DRISK=Division of Risk Management

CDTL=Cross Discipline Team Leader

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

The objective of NDA 022474 is to obtain marketing approval for ella (ulipristal acetate) tablet, an emergency contraceptive “*indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. Ella is not intended for routine use as a contraceptive.*” The proposed dosing regimen is one tablet (30 mg of ulipristal acetate, also referred to as ulipristal) taken orally as soon as possible, within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure. (The abbreviation “UPI” as used in this Review will refer to both unprotected intercourse and a contraceptive failure.) Ulipristal is an orally-active progesterone agonist/antagonist, also referred to as a selective progesterone receptor modulator. It currently is not available in any drug product approved in the US and is a new molecular entity (NME). If approved, ella would extend the availability of emergency contraception (EC) from 3 days (72 hours) after UPI for currently approved levonorgestrel-based EC products (e.g., Plan B) to 5 days (120 hours). Ulipristal, under the proprietary name of ellaOne[®], was approved by the European Medicines Agency (EMA) for marketing in May 2009. It is currently marketed in over 20 countries.

This Application contained the necessary chemistry, manufacturing and controls (CMC), preclinical toxicology, and clinical pharmacology information to support approval. The Applicant conducted two Phase 3 clinical trials (one entirely in the US) to support the clinical safety and efficacy of ulipristal (30 mg) for the proposed indication. No significant preclinical or clinical approvability issues were identified during the review of NDA 022474. All discipline reviewers, including the primary Clinical Reviewer (Dr. Orleans) and the Clinical Team Leader (Dr. Soule), have recommended that ulipristal be approved for the proposed indication. The Application also was discussed at a meeting of the Advisory Committee for Reproductive Health Drugs. The Committee members were unanimous in concluding that the Applicant had provided sufficient efficacy and safety data to support the proposed indication. I concur with the recommendations of the discipline reviewers as well as the overall assessment of the Advisory Committee. I recommend that ella (ulipristal acetate) tablet be approved for *prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.*

2. BACKGROUND

2.1 Description of the Product

Ulipristal acetate is an orally-active progesterone agonist/antagonist with antagonistic and partial agonistic effects at the progesterone receptor. Ulipristal binds the human progesterone receptor and prevents progesterone from occupying its receptor. If approved, ella will be supplied as a single tablet in a blister pack. Each tablet contains 30 mg of micronized ulipristal acetate. Ulipristal currently is not available in any US approved drug product and is a NME.

The pharmacodynamics of ulipristal depends on the timing of administration during the menstrual cycle. Administration in the mid-follicular phase causes inhibition of folliculogenesis and reduction of estradiol concentration. Administration at the time of the luteinizing hormone (LH) peak delays follicular rupture by 5 to 9 days. Dosing in the early luteal phase does not significantly delay endometrial maturation but decreases slightly endometrial thickness.

The likely primary mechanism of action of ulipristal for EC is inhibition or delay of ovulation; alterations of the endometrium that could impair implantation also may contribute to its efficacy as an emergency contraceptive.

2.2 Regulatory History

Ulipristal was developed under IND 49,381, which was opened in 1995. The original IND holder, the National Institute of Child Health and Human Development (NICHD), transferred the IND in January 2006 to the current holder, HRA Pharma. Several meetings were held with both IND holders dating back to 1996. A detailed description of the regulatory history is provided in the CDTL review, signed on August 13, 2010.

Division Director's Comment

- *The two Phase 3 clinical trials that are the primary source of the efficacy and safety data in support of the proposed EC indication were conducted in accordance with the guidance that the Division of Reproductive and Urologic Products (DRUP) provided to the Applicant.*

2.3 Content of NDA

The Application contained the necessary CMC, preclinical toxicology, and clinical pharmacology information to support approval. The primary clinical support for the safety and efficacy of ulipristal 30 mg tablet for EC is based on two Phase 3 clinical trials (Study HRA2914-509 and Study HRA2914-513) conducted by the Applicant with the to-be-marketed micronized formulation. Supportive safety and efficacy Phase 2 data, obtained with a non-micronized formulation of ulipristal, also were provided.

2.4 Recommendations of Primary Clinical Reviewer and Cross-Discipline Team Leader regarding Approvability

The primary Clinical Reviewer, Ronald Orleans MD, stated the following in his Clinical Review signed on August 6, 2010:

“The risk benefit ratio of ulipristal acetate for use as emergency contraception up to 120 hrs after intercourse at the dose of 30 mg appears favorable. If approved, this would be the only hormonal emergency contraceptive shown to be effective beyond 72 hours of UPI. This five day window of efficacy combined with an acceptable safety profile makes this a unique medication for the indication of emergency contraception.”

“At a meeting held on June 17, 2010, the Advisory Committee for Reproductive Health Drugs unanimously voted that there was sufficient safety and efficacy data to recommend marketing approval for the indication of emergency contraception up to 120 hours after unprotected intercourse. I concur with the Committee’s opinion and also recommend approval of ulipristal for the indication sought.”

Dr. Orleans also recommended the Applicant conduct the postmarketing studies that are listed in Section 13.4 of this Review.

The Cross Discipline Team Leader (CDTL), Lisa Soule MD (who also was the Clinical Team Leader), stated the following in her Review signed on August 13, 2010:

"I recommend that ulipristal acetate be approved for the indication 'prevention of pregnancy following unprotected intercourse or known or suspected contraceptive failure,' with the drug to be taken within 120 hours after the act of intercourse of concern."

"Ulipristal demonstrated compelling efficacy as an emergency contraceptive in two trials, and according to two co-primary efficacy endpoints and several secondary endpoints. Ulipristal was shown to be non-inferior to the approved emergency contraceptive LNG 1.5 mg, and showed a non-statistically significant trend toward a greater prevented fraction of pregnancies."

"Overall, the use of ulipristal for the prevention of pregnancy following UPI or a known or suspected contraceptive failure, therefore, has a favorable risk/benefit profile."

Division Director's Comment

- *I concur with the recommendations of both Drs. Orleans and Soule that ulipristal be approved as an emergency contraceptive for "prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure."*

3. CMC

The primary Chemistry Reviewer, Bogdan Kurtyka PhD, made the following statement in the Recommendation and Conclusion on Approvability section of his CMC Review signed on June 25, 2010:

"This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. An overall "Acceptable" site recommendation has been made from the Office of Compliance.

However, issues on labels/labeling have not been resolved. Therefore, from a CMC perspective, this NDA is not recommended for "Approval" in its present form."

Dr. Kurtyka found the Applicant's claim for categorical exclusion from environmental assessment to be acceptable. He did not recommend any Phase 4 commitments.

In an Addendum (signed on August 12, 2010) to his original primary CMC Review, Dr. Kurtyka made the following statement and final recommendation:

"The sponsor submitted the updated labeling on 12-AUG-2010 and addressed above issues satisfactorily.

Therefore, from a CMC perspective, NDA 22-474 is now recommended for 'Approval'."

Division Director's Comment

- *I concur with the assessments and final recommendation by Dr. Kurtyka that from a CMC perspective this NDA can be approved.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The nonclinical program for ulipristal included pharmacology studies, pharmacokinetic and toxicokinetic studies, general toxicology studies, acute and chronic (6 month) toxicology studies, genotoxicity studies, and reproductive toxicity studies. Repeat dose toxicity studies in rats and

monkeys showed the expected pharmacological effects of an antiprogesterin/antiglucocorticoid agent. The predominant organ systems affected in both species were reproductive and endocrine (e.g., the ovary, mammary gland, uterus, adrenal, and pituitary), with less effects on the liver.

The *in vitro* and *in vivo* genotoxicity assays were negative for mutagenicity and clastogenicity. Carcinogenicity testing in rats is currently ongoing, but a computational toxicity consult was requested. The consult response concluded that

“In considering the entire weight of evidence, ICSAS concludes that Ulipristal acetate is predicted to be negative for both rat and mouse carcinogenicity.”

The pharmacologic effects of ulipristal in nonclinical studies include dose-dependent inhibition of ovulation, pregnancy, and implantation rates. Single oral doses of ulipristal prevented ovulation in 50% of rats at 2 times the human exposure based on body surface area (mg/m^2). Single doses of ulipristal 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 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 daily drug exposures 1/3 and 1/2 the human exposure, respectively, based on body surface area (mg/m^2). There were no malformations of the surviving fetuses in these studies. Adverse effects were not observed in the offspring of pregnant rats administered ulipristal daily during the period of organogenesis through lactation at drug exposures 1/24 the human exposure based on AUC.

The ability of a single dose of ulipristal to interrupt an established pregnancy was not studied in the nonclinical program. Administration of ulipristal to pregnant monkeys for 4 days during the first trimester did not cause pregnancy termination in any of 5 animals dosed at 0.5 mg/kg/day, but caused pregnancy termination in 2/5 animals dose at 5 mg/kg/day (a daily exposure estimated to be 3 times the human exposure based on body surface area).

The primary Toxicology Reviewer, Jeffrey Bray, Ph.D., made the following recommendations in his Review signed on June 28, 2010:

Recommendations on approvability: Yes. Pharmacology recommends approval for emergency contraception for up to 120 hours following unprotected sexual intercourse.

Recommendations for nonclinical studies: None.

Recommendations on labeling: Nonclinical labeling in sections 8.1, 8.3, 13.1 and 13.2 require modification.

In an Addendum (signed on August 13, 2010) to his original primary review, Dr. Bray made the following statement:

“Pharm/Tox has reviewed the final submitted labeling and finds it acceptable.”

Division Director's Comment

- *I concur with the conclusions and recommendations of Dr. Bray.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

The Applicant submitted 16 clinical pharmacology studies. These included 8 studies of the distribution, metabolism, and drug interaction potential of ulipristal, 4 pharmacokinetic (PK), and 4 pharmacodynamic (PD) studies. These studies were reviewed by the primary Clinical Pharmacology Reviewer, Hyunjin Kim, PharmD.

When ulipristal was under development by the NICHD, the drug formulation consisted of non-micronized ulipristal in capsules. The initial pharmacology program and the Phase 2 clinical trials were conducted using this non-micronized formulation. After HRA Pharma licensed the rights to the compound, micronization was added as the last step of the manufacturing process. The micronized product was found to have a higher bioavailability. It was the formulation used in the two Phase 3 clinical trials, and it is the formulation that will be used in the to-be-marketed product.

5.1 Pharmacokinetics

Ulipristal is metabolized to mono-demethylated and di-demethylated metabolites. *In vitro* data indicate that this is predominantly mediated by CYP3A4. The mono-demethylated metabolite is pharmacologically active. Ulipristal is highly bound (> 94%) to plasma proteins, including high density lipoprotein, alpha-1-acid glycoprotein, and albumin.

Following oral administration of ulipristal, maximum plasma concentrations of ulipristal and its active metabolite, monodemethyl-ulipristal acetate are observed at approximately one hour. The terminal half-life of ulipristal in plasma following a single 30 mg oral dose is estimated to be 32.4 ± 6.3 hours.

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

5.2 Pharmacodynamics

The pharmacologic action of ulipristal is mediated by its binding to the progesterone receptor. A number of studies were conducted to assess the effects of a single dose of ulipristal administered at different phases of the menstrual cycle. The pharmacodynamics of ulipristal depends on the timing of administration within the menstrual cycle. Administration in the mid-follicular phase causes inhibition of folliculogenesis and reduction of estradiol concentration. Administration at the time of the luteinizing hormone (LH) peak delays follicular rupture by 5 to 9 days. Dosing in the early luteal phase does not significantly delay endometrial maturation but decreases slightly endometrial thickness.

5.3 Overall Assessment by Clinical Pharmacology Reviewer

Dr. Kim stated the following in his Clinical Pharmacology Review signed on July 9, 2010:

“The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 022474 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert.”

Clinical pharmacology also requested that the Applicant conduct an *in vivo* drug-drug interaction study of ulipristal with a CYP3A4 inducer as a Postmarketing Commitment (PMC). This request was made because of the potential for CYP3A4 inducers to reduce significantly plasma concentrations of ulipristal, and thereby also reduce its effectiveness. The Applicant agreed to conduct such a study.

In an Addendum (signed on August 12, 2010) to his original review, Dr. Kim made the following statement:

“The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 022474 acceptable.”

Division Director’s Comment

- *I concur with Dr. Kim’s overall assessment.*

6. CLINICAL MICROBIOLOGY

A microbiology consult was not needed for this oral tablet; Dr. Kurtyka concluded that the manufacturing processes for the solid oral dosage form are conducted in accordance with cGMPs to prevent microbial contamination.

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Phase 3 Clinical Trials – Objectives and Design

The primary sources of the clinical efficacy and safety data in support of approval of ulipristal for EC were two Phase 3 clinical trials (HRA2914-509 and HRA2914-513) (see Table 1). Study HRA2914-509 (also referred to as Study 509) was a prospective, multicenter, open-label, single-arm trial, conducted in the US. The study evaluated the efficacy and safety of a single 30 mg dose of ulipristal administered 48 to 120 hours after UPI in women ages 18 years and older with regular menstrual cycles seeking EC. Study HRA2914-513 (also referred to as Study 513) was a prospective, multicenter, randomized, single-blind, parallel group, comparative trial, conducted in the United Kingdom, Ireland, and the US. The study evaluated the efficacy and safety of a single 30 mg dose of ulipristal, compared to levonorgestrel (LNG) 1.5 mg, administered 0 to 120 hours after UPI in women ages 16 years and older with regular menstrual cycles seeking EC.

Table 1 Overview of Phase 3 Clinical Trials of Ulipristal for Emergency Contraception

Study Number (# sites/ Country)	Design	Study Population	Primary Endpoint	Treatment	ITT (mITT)
HRA2914-509 (40/US)	Prospective, Multicenter, Open label	Women ≥ 18 years old, regular cycle length (24 to 35 days), presenting for EC between 48 to 120 hours after UPI	Pregnancy Rate	Ulipristal 30 mg	1,533 (1,241)
HRA2914-513 (24/US,10/UK, 1/Ireland)	Prospective, Multicenter, Randomized, Single blind, Parallel group	Women ≥ 16 years old, regular cycle length (24 to 35 days), presenting for EC between 0 to 120 hours after UPI	Pregnancy Rate *	Ulipristal 30 mg	1,104 (941)
				LNG 1.5 mg	1,117 (958)
				Total	2,221 (1,899)

*Because the active control was levonorgestrel (LNG), the time frame for the primary efficacy analysis covered the period of 0 to 72 hours after UPI (the approved window for use of LNG for EC).

Source: Table 4 of FDA Background Document (dated May 20, 2010) for the Meeting of the Advisory Committee for Reproductive Health Drugs (June 17, 1020),

7.1.1 Study HRA2914-509

7.1.1.1 Study Objectives

The primary objective of the study was to demonstrate that the pregnancy rate observed after taking 30 mg ulipristal between 48 hours and 120 hours after UPI was statistically significantly lower than the estimated expected pregnancy rate in the study population in the absence of EC.

Secondary objectives were to:

1. Demonstrate that the pregnancy rate observed after taking ulipristal between 48 and 120 hours after UPI was statistically significantly lower than the Applicant's 4% clinical relevance threshold.
2. Analyze the trend in pregnancy rates over time based on the time between UPI and administration of ulipristal.
3. Estimate the contraceptive effectiveness of ulipristal based on the prevented fraction of expected pregnancies.

Division Director's Comment

- *The clinical relevance threshold of 4% represented a 50% reduction of the expected 8% pregnancy rate in the absence of contraception that had been observed in previous studies of EC. The 4% threshold was thought by the Applicant to represent a clinically meaningful reduction in the pregnancy rate.*

7.1.1.2 Trial Design

This was a prospective, open-label, single-arm trial conducted at 40 Planned Parenthood family planning clinics, all located in the US. Women at least 18 years of age, with regular menstrual cycles (length between 24 and 35 days), who presented requesting EC between 48 and 120 hours after UPI and who met other inclusion/exclusion criteria were enrolled into the study. A total of up to 3 visits were scheduled over the course of the study: Day 1 (screening and treatment visit) followed by up to 2 follow-up visits approximately 7 and 14 days after the subject's expected

menses. Because no EC product is currently approved to be taken more than 72 hours after UPI, no active control was used in this study.

7.1.1.3 Analysis Populations

The Applicant's definitions for the various analysis populations included:

1. **Intent-To-Treat (ITT) Population** (also the Safety Population) consisted of all subjects who received EC. Repeat enrollers were included in this population and treated as independent subjects in the analysis.
2. **Intent-To-Treat (ITT) Completers** consisted of all ITT subjects who met the following additional criteria:
 - participating for the first time in the current study (i.e., repeat enrollers were not included).
 - with a known pregnancy status (i.e., pregnant or not pregnant) after EC intake (as stated by the investigator in the study completion form).
3. **Modified Intent-To-Treat (mITT) Population** consisted of all ITT Completers who met the following additional criteria:
 - age \leq 35 years.
 - post treatment pregnancy NOT identified as having been conceived before EC intake (as assessed by a positive pre-treatment serum β -hCG and gestational age confirmation by transvaginal ultrasound) or as "not compatible" with an EC failure, based on an independent evaluation by the Data Safety Monitoring Board (DSMB).

Division Director's Comment

- *The Applicant considered the mITT population to be the primary efficacy analysis population. DRUP independently reviewed all cases classified by the applicant or DSMB as "not compatible" with an EC failure. In some instances, the DRUP clinical reviewers did not believe that the data warranted exclusion of a subject from the primary efficacy population. This latter population, referred to as the "FDA efficacy population" in this document, was used in DRUP's assessment of efficacy. Differences between the Applicant's mITT population and the FDA efficacy population, when present, were small.*
- *Unless otherwise indicated, all conclusions presented in this Summary Review are based on the FDA efficacy populations for Study HRA2914-509 and Study HRA2914-513.*

7.1.2 Study HRA2914-513

7.1.2.1 Study Objectives

The primary objective of this study was to demonstrate that the pregnancy rate observed after taking 30 mg ulipristal within 72 hours after UPI was statistically significantly lower than the estimated expected pregnancy rate in the study population in the absence of EC.

Secondary objectives included to:

1. Demonstrate that the pregnancy rate observed after taking ulipristal within 72 hours of UPI was statistically significantly lower than the Applicant's 4% clinical relevance threshold.
2. Demonstrate that ulipristal was non-inferior to 1.5 mg LNG when taken within 72 hours of UPI. Should non-inferiority be demonstrated, superiority would be tested.

3. Analyze the trend in pregnancy rates over time based on the time between UPI and administration of ulipristal or LNG.
4. Estimate the contraceptive effectiveness of ulipristal and LNG based on the prevented fraction of expected pregnancies.

7.1.2.2 Trial Design

This was a randomized, comparative, two-arm parallel group, single blind (subjects and sponsor blinded and investigator unblinded), multicenter study, conducted in the US and Europe. Women (aged ≥ 16 years in the United Kingdom (UK), ≥ 17 years in Ireland, and ≥ 18 years in the US), with regular menstrual cycles (length between 24 and 35 days) who presented requesting EC between 0 and 72 hours after UPI and who met the other inclusion/exclusion criteria were enrolled into the study. Women presenting more than 72 hours and no later than 120 hours after UPI were eligible for inclusion only if they declined the insertion of an intrauterine device (IUD) for EC or had contraindications to the use of an IUD. Subjects were randomized to treatment with a single dose of 30 mg ulipristal or 1.5 mg LNG (active comparator). The study was performed at 10 centers in the UK, one center in Ireland, and 24 centers in the US. Other aspects of the trial design were similar to those for Study HRA2914-509.

7.1.2.3 Analysis Populations

The analysis populations were the same as those in Study HRA2914-509.

7.2 Demographics –Phase 3 Trials

The demographics and baseline characteristics of the ITT populations in Study HRA2914-509 and Study HRA2914-513 are presented in Table 2.

In Study HRA2914-509, the mean (\pm SD) age of the 1,533 subjects in the ITT population was 24.4 ± 6.1 years. Most subjects were in the 18 to 25 years age group (69%); approximately 94% of subjects were between the ages of 18 and 35 years. The majority of subjects were White (60.3%), with African American subjects constituting the second largest group (21.5%).

In Study HRA2914-513, the 2 treatment groups were very similar. The mean age was approximately 25 years, with about 4% of the population < 18 years old in both treatment groups. The majority of participants were White (~73%) with African American subjects comprising about 19% of subjects.

Table 2 Demographics and Baseline Characteristics (ITT Populations)

Variable	HRA2914-509	HRA2914-513	
	(N=1,533)	Ulipristal N=1,104	Levonorgestrel N=1,117
Age (Years) (Mean ± SD)	24.4 ± 6.1 Min-Max=18-50	24.5 ± 6.1 Min-Max: 16-52	24.9 ± 6.5. Min-Max: 16-55
Age Category			
16-17	0%	4.0%	4.4%
18-35	93.5%	89.5%	88.2%
36 and older	6.5%	6.5%	7.4%
Race			
White	60.3%	72.8%	72.4%
African American	21.5%	19.0%	18.5%
Asian	2.3%	1.2%	1.9%
Other	13.9%	7.0%	7.2%
Body Mass Index (kg/m ²)	25.3 ± 6.2 Min-Max=16.1-61.3	25.3 ± 5.9 Min-Max: 15.8-70.0	25.2±5.7 Min-Max: 14.9-53.7

Source: Modified from Table 4 of the primary Clinical Review signed August 6, 2010.

7.3 Efficacy Analyses

7.3.1 Primary Endpoint and Analysis

Primary Efficacy Endpoint

The primary efficacy endpoint was the **pregnancy rate**, defined as the number of pregnancies occurring after taking ulipristal (or LNG) for EC divided by the number of subjects who took ulipristal (or LNG).

Primary Efficacy Analysis

The primary efficacy analysis compared the upper bound of the 95% confidence interval (CI) of the point estimate of the observed pregnancy rate in subjects who took EC to the estimated expected pregnancy rate in the absence of EC. The estimated expected pregnancy rate was calculated according to the method of Trussell et al. using a pooled set of conception probabilities and the estimated cycle day of UPI (see conception probabilities in Table 3).

The cycle day of UPI (cycle day relative to day of ovulation) for each subject was determined as follows:

$$\text{Cycle day of UPI} = (\text{Date of UPI} - \text{Date of first day of last menstrual period} + 1) - (\text{Average length of menstrual cycle} - 14)$$

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Source: Trussell J, Rodriguez G, Ellertson C. New Estimates of the Effectiveness of the Yuzpe Regimen of Emergency Contraception. Contraception 1998;57:363-9.

The observed pregnancy rate was to be declared statistically significantly lower than the estimated expected pregnancy rate if the upper bound of the 2-sided 95% CI of the observed pregnancy rate was below the estimated expected pregnancy rate.

7.3.2 Secondary Analyses and Endpoints

Main Secondary Efficacy Analysis

The main secondary efficacy analysis was the determination of non-inferiority of the observed pregnancy rate in subjects treated with ulipristal (or LNG) compared to the Applicant's clinical relevance threshold of a 4% pregnancy rate. Ulipristal (or LNG) was to be declared non-inferior to this clinical threshold if the upper limit of the 2-sided 95% CI of the observed pregnancy rate was lower than 4%. The clinical trial was to be considered as a success if both the primary efficacy analysis and the main secondary analysis (non-inferiority to the clinical relevance threshold of 4%) demonstrated efficacy for ulipristal in the Applicant's mITT population.

Division Director's Comment

- *Because the Applicant's statistical analysis plan specified that the study would be considered a success if both the primary efficacy analysis and main secondary efficacy analysis were successful, DRUP considered these analyses as co-primary analyses.*

Additional Secondary Efficacy Analyses

1. **Prevented fraction of pregnancies.** The prevented fraction of pregnancies was defined as the number of prevented pregnancies divided by the number of estimated expected pregnancies, where the number of prevented pregnancies was calculated as follows:

$$\text{Number of prevented pregnancies} = \text{Number of estimated expected pregnancies} - \text{Number of observed pregnancies}$$

2. **Trend in pregnancy rates over time.** Pregnancy rates, based on the actual time between UPI and the subject's taking ulipristal, were calculated for each 24-hour period over the interval of interest (either 72-120 hours or 0-120 hours after UPI).

7.4 Efficacy Findings

7.4.1 Study HRA2914-509

7.4.1.1 Subject Enrollment and Disposition

A total of 1,533 were treated and were included in the ITT population. Of these subjects, 292 subjects (19%) were excluded from the mITT population for the following reasons:

- Unknown pregnancy status after enrollment n=106 (6.9%)
- Repeat enrollment n=84 (5.5%)
- Greater than 35 years of age n=99 (6.5%)
- Pregnancy not attributable to EC failure n=3 (0.2%)

The Applicant's mITT population consisted of 1,241 subjects and included 26 pregnancies that were considered to represent EC failures. The DRUP reviewers, however, concluded that only 2 pregnancies (in contrast to the Applicant's 3 pregnancies) were not attributable to EC failure and the FDA efficacy population consisted of 1,242 subjects and 27 observed pregnancies.

7.4.1.2 Primary Efficacy Results

The results of the primary efficacy analysis, the pregnancy rate, based on the Applicant's mITT population and the FDA efficacy population for subjects treated between 48 and 120 hours after UPI are shown in Table 4. Based on the FDA efficacy population, the observed pregnancy rate was 2.17% (95% CI: 1.47%, 3.19%). The upper bound of the 95% CI (i.e., 3.19%) did not exceed the calculated expected pregnancy rate of 5.53% or the clinical relevance threshold of 4%.

Table 4 Pregnancy Rates in Subjects Taking Ulipristal 48-120 Hours after UPI (Study HRA2914-509)

	Applicant's mITT Population N=1241	FDA Efficacy Population N=1242
Estimated Expected Pregnancies per Trussell (n)	69	69
Estimated Expected Pregnancy Rate (%)	5.53%	5.53%
Observed Pregnancies (n)	26	27
Observed Pregnancy Rate (%) (95% CI)	2.10% (1.41, 3.10)	2.17% (1.47, 3.19)

Source: Table 8 of FDA Statistical Review, signed July 22, 2010.

Division Director's Comment

- *The upper bound of the 95% CI (i.e., 3.19%) did not exceed the calculated expected pregnancy rate of 5.53% or the clinical relevance threshold of 4%. Therefore, the results support the efficacy of ulipristal in reducing the risk of pregnancy when taken within 48-120 hours after UPI.*

7.4.1.3 Secondary Efficacy Results

Trend in Pregnancy Rates over Time

The findings for the trend in pregnancy rates over time are presented in Table 9 as pooled results with the findings from Study HRA2914-509.

Prevented Fraction

The proportions of pregnancies prevented by treatment with ulipristal 48 to 120 hours after UPI based on the Applicant's mITT and the FDA efficacy population are presented in Table 5. Treatment with ulipristal prevented 60.9% of the expected pregnancies.

Table 5 Prevented Fraction of Pregnancies in Subjects Taking Ulipristal 48-120 Hours after UPI (Study HRA2914-509)

Population	Subjects Exposed (N)	Observed Pregnancies (n)	Expected Pregnancies (n)	Prevented Fraction (%, 95% CI)
Applicant's mITT	1241	26	69	62.3 (41.9, 75.6)
FDA Efficacy Population	1242	27	69	60.9 (40.1, 74.5)

Source: Table 9 of FDA Statistical Review, signed July 22, 2010.

7.4.2 Study HRA2914-513

7.4.2.1 Subject Enrollment and Disposition

A total of 1,104 and 1,117 subjects were treated with ulipristal or LNG, respectively, over the interval of 0-120 hours after UPI. Of these subjects, 163 and 159 subjects were excluded from the Applicant's ulipristal or LNG mITT populations, respectively, for the following reasons:

	Ulipristal group (n)	LNG group (n)
• Unknown pregnancy status after enrollment	77	57
• Repeat enrollment	14	22
• Greater than 35 years of age	69	76
• Pregnancy not attributable to EC failure	3	4

7.4.2.2 Primary Efficacy Results

A pre-specified interim analysis was to be performed on the first 1,200 mITT subjects who took study drug within 72 hours after UPI. If the interim analyses met 3 criteria for success, enrollment into the clinical trial was to be terminated. Should this be the case, per the Applicant's Statistical Analysis Plan, the primary efficacy outcomes would be based on the "interim" analysis. At the time of completion of the interim analysis, the study was close to completion. Therefore, data from these latter subjects who were not included in the interim analysis, in conjunction with the data from the subjects included in the interim analysis, were combined to form the final (or complete) database.

Division Director's Comment

- *Efficacy analyses based on the final or complete study population were considered as supportive analyses per the Applicant's pre-specified analysis plan. DRUP concurred with this decision.*

Primary Analysis (Interim Population)

The results of the primary efficacy analysis based on the interim mITT population are presented in Table 6. In the ulipristal treatment group, the observed pregnancy rate (based on 9 observed pregnancies) in the interim mITT population (N = 596) was 1.51% (95% CI: 0.62%, 3.32%). This observed pregnancy rate was statistically significantly lower than the calculated expected pregnancy rate of 5.63% and lower than the clinical relevance threshold of 4%. In the LNG treatment group, there were 17 confirmed pregnancies in the interim mITT population (N = 604), and the observed pregnancy rate was 2.81% (95% CI: 1.54%, 4.97%).

Table 6 Pregnancy Rates in Subjects Taking Ulipristal or Levonorgestrel 0-72 Hours after UPI (Study HRA2914-513, Interim mITT Population*)

	Ulipristal acetate N=596	Levonorgestrel N=604
Estimated Expected Pregnancies per Trussell (n)	33	36
Estimated Expected Pregnancy rate (%)	5.63%	5.88%
Observed Pregnancies (n)	9	17
Observed Pregnancy rate (%) (95% CI) *	1.51% (0.62-3.32)	2.81% (1.54-4.97)

* The Applicant's interim mITT and the interim FDA efficacy populations were identical.

Source: Table 15 of FDA Statistical Review, signed July 22, 2010.

Supportive Analysis (Final Population)

The final (or complete) study database (Final FDA efficacy population) included 16 and 22 pregnancies attributed to EC failure in subjects ≤ 35 years of age in the ulipristal and LNG treatment groups, respectively (see Table 7). The observed pregnancy rates were 1.90% (CI: 1.13%, 3.12%) and 2.59% (CI: 1.68%, 3.94%) in the ulipristal and LNG treatment groups, respectively. The observed pregnancy rate in each treatment group was statistically significantly lower than the estimated expected pregnancy rate in the respective treatment group (ulipristal: 5.55%, LNG: 5.43%). The upper limit of the 2-sided 95% CI of the observed pregnancy rate also was lower than the Applicant's clinical relevance threshold of 4% for both treatment groups.

Table 7 Pregnancy Rates in Subjects Taking Ulipristal or Levonorgestrel 0-72 hours after UPI (Study HRA2914-513, Final FDA Efficacy Population)

	Ulipristal acetate N=844	Levonorgestrel N=851
Expected Pregnancies per Trussell (n)	47	46
Expected Pregnancy Rate (%)	5.55%	5.43%
Observed Pregnancies (n)	16	22
Observed pregnancy rate (%) (95% CI)	1.90% (1.13, 3.12)	2.59% (1.68, 3.94)

Source: Table 16 of FDA Statistical Review, signed July 22, 2010.

Division Director's Comment

- In both of the analyses (i.e., that based on the interim population and that based on the final or complete population), ulipristal met the pre-specified criteria for success. The observed pregnancy rates were statistically significantly lower than the estimated expected pregnancy rates and the upper limits of the 2-sided 95% CI of the observed pregnancy rates were lower than the Applicant's clinical relevance threshold of 4%.*

7.4.2.3 Secondary Efficacy Results

Non-inferiority of Ulipristal to LNG

For the interim mITT population, ulipristal was non-inferior to LNG when taken within 72 hours of UPI (odds ratio for pregnancy: 0.53) as the upper bound of the 95% CI of the odds ratio (1.44) was lower than the protocol-defined non-inferiority margin of 1.6 (see Table 8). Superiority,

however, was not established because the upper bound of the 95% CI of the odds ratio crossed 1.0.

Table 8 Odds Ratio for Pregnancy Rate of Ulipristal Relative to Levonorgestrel: Subjects Taking Ulipristal or Levonorgestrel 0-72 Hours after UPI (Study HRA2914-513, Interim FDA Efficacy Population*)

	Ulipristal acetate N=596	Levonorgestrel N=604
Observed Pregnancy (n)	9	17
Observed Pregnancy Rate (%)	1.51	2.81
Odds Ratio (95% CI)	0.53 (0.20, 1.44)	

* The Applicant's interim mITT and the interim FDA efficacy populations are identical.

Source: Table 20 of FDA Statistical Review, signed July 22, 2010.

7.4.3 Secondary Efficacy Analyses (Pooled Data)

Effect of Age

Subgroup analyses of pregnancy rates by age group (< 18, 18 to 35, and > 35 years old) for Study HRA2914-513 individually and pooled with Study HRA2914-509 were performed. There was no apparent effect of age on the efficacy of ulipristal in either analysis, although the results are not definitive due to the small sample sizes in the < 18 and > 35 year subgroups (< 18 years old: N=34; > 35 years old: N=159).

Trend in Pregnancy Rates over Time

Observed and estimated expected pregnancy rates were determined for the five 24-hour intervals from 0-120 hours between UPI and ulipristal treatment using pooled data from the two Phase 3 studies. The results of the analysis, based on the FDA efficacy populations for Studies HRA2914-509 and HRA2914-513 (final population) are shown in Table 9. There were no apparent differences in the observed pregnancy rates or prevented fractions of pregnancies across the 5 time intervals.

Table 9 Trend Analysis for Pregnancy Rates by 24-hour Intervals between UPI and Taking Ulipristal (Pooled Phase 3 Studies*)

Time from UPI (hours)	Observed Pregnancies (n)	Exposed Subjects (n)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancies (n)	Expected Pregnancy Rate (%)	Prevented Fraction (%) (95 CI)
0 - 24	5	312	1.60 (0.56, 3.88)	15	4.73	66.7 (19.2, 86.2)
25 - 48	7	329	2.13 (0.92, 4.49)	19	5.86	63.2 (20.5, 82.9)
49 - 72	21	898	2.34 (1.50, 3.60)	55	6.09	60.4 (36.6, 75.2)
73 - 96	8	453	1.77 (0.82, 3.56)	24	5.30	65.2 (28.3, 83.1)
97 -120	2	190	1.05 (0.02, 4.12)	10	5.10	77.8 (12.0, 94.4)
0 - 120	43	2,182	1.97 (1.45, 2.67)	122	5.61	63.9 (48.3, 74.7)

* The analysis population for study HRA2914-509 is the FDA efficacy population and that for Study HRA2914-513 is the Final FDA efficacy population.

Source: Table 21 of FDA Statistical Review, signed July 22, 2010.

Effect of Body Mass Index on Efficacy

Observed and estimated expected pregnancy rates by BMI ($\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) are presented for each of the Phase 3 studies as well as for the pooled Phase 3 data (see Table 10). In women with BMI $> 30 \text{ kg/m}^2$, the upper limits of the 95% CIs were consistently greater than the respective expected pregnancy rate and higher than the clinical relevance threshold of 4%, suggesting reduced efficacy for both ulipristal and LNG in this subgroup.

Table 10 Pregnancy Rates by Body Mass Index (BMI, $\leq 30 \text{ kg/m}^2$ or $> 30 \text{ kg/m}^2$) for Ulipristal and Levonorgestrel (Studies HRA2914-509 and HRA2914-513, FDA Efficacy Populations)

Study / Time Window	BMI Subgroup (kg/m ²)	Ulipristal acetate			Levonorgestrel		
		Pregnancies / Subjects (n / N)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancy Rate (%)	Pregnancies / Subjects (n / N)	Observed Pregnancy Rate (%) (95% CI)	Expected Pregnancy Rate (%)
HRA2914-509 48 - 120	BMI ≤ 30	21 / 1035	2.03 (1.30, 3.13)	5.76	NA		
	BMI > 30	6 / 207	2.90 (1.15, 6.45)	4.37			
HRA2914-513 0 - 72	BMI ≤ 30	11 / 717	1.53 (0.81, 2.80)	5.71	12 / 716	1.68 (0.91, 2.98)	5.63
	BMI > 30	5 / 127	3.94 (1.41, 9.29)	4.61	10 / 135	7.41 (3.86, 13.42)	4.38
Pooled 0 - 120	BMI ≤ 30	32 / 1832	1.75 (1.22, 2.48)	5.83	14 / 800	1.75 (1.00, 2.98)	5.71
	BMI > 30	11 / 350	3.14 (1.67, 5.68)	4.48	11 / 154	7.14 (3.85, 12.6)	4.53

Source: Table 27 of FDA Statistical Review, signed July 22, 2010.

Division Director's Comments

- *The conclusions that can be made regarding the efficacy of ulipristal in women with a BMI > 30 kg/m² are limited somewhat by the relatively small sample size (i.e., only approximately 16% of subjects treated with ulipristal had a BMI > 30 kg/m²). The small sample size likely contributed to the wide 95% CIs.*
- *The effect of BMI on the observed pregnancy rates in subjects treated with LNG within 72 hours after UPI appeared to be greater than that in ulipristal-treated subjects. For women with a BMI > 30 kg/m² who received LNG within 72 hours after UPI in Study HRA2914-513, the upper bound of the 95% CI for the observed pregnancy rate (13.42%) also was greater than the estimated expected pregnancy rate of 4.38%.*

7.5 FDA Statistician's Assessment of Efficacy

The statistical reviewer, Kate Dwyer, Ph.D., confirmed the Applicant's primary efficacy findings. As noted previously, the efficacy population used by FDA was not identical to that used by the Applicant because the FDA clinical reviewers did not agree with all decisions made by the Applicant as to which pregnancies were "not compatible" with EC failure. Although the FDA efficacy populations for ulipristal included 1 or 2 additional pregnancies compared to that of the Applicant, the overall conclusions, based on the analyses of the different populations, were the same. In the Executive Summary of her Statistical Review, signed on July 22, 2010, Dr. Dwyer made the following statements:

"Data support the efficacy of Ulipristal acetate 30 mg as an emergency contraception (EC) within 120 hours after unprotected intercourse (UPI). The observed pregnancy rates for treatment with Ulipristal administered within 120 hours after UPI in two studies were statistically lower than the expected rates in the absence of EC and lower than the clinical relevance threshold of 4%."

"Both studies had reasonable dropout rates and recruited an adequate number of subjects for the planned effect size to assess the efficacy of the doses under investigation with at least 80% power."

7.6 Overall Assessment of Efficacy

Both Phase 3 studies demonstrated that treatment with ulipristal administered within 120 hours after UPI resulted in an observed pregnancy rate that was (1) statistically lower than the expected pregnancy rate in the absence of EC and (2) lower than the Applicant's prespecified clinical relevance threshold of 4%. Similar efficacy results were observed in the primary analysis using different analysis populations (e.g., applicant's mITT populations and FDA efficacy populations). Results of secondary efficacy analyses also supported the findings of the primary analyses. No effect of age on the efficacy of ulipristal was observed. The efficacy of ulipristal remained consistent regardless of the time interval between UPI and treatment for up to 120 hours after UPI. The effectiveness of ulipristal (as well as LNG for EC), however, appeared to be reduced in subjects with a BMI > 30 kg/m².

8. SAFETY

The following Summary Review of safety findings focuses on findings from the two large Phase 3 studies that investigated the to-be-marketed 30 mg ulipristal tablet. A comprehensive safety review is presented in the primary Clinical Review.

8.1 Overview of Safety Database for Ulipristal

The ulipristal safety database includes data from nine Phase 1 PK/PD studies, two Phase 2 studies, and two Phase 3 studies. All studies, with the exception of one Phase 1 study, used single doses of ulipristal. Four of the Phase 1 studies and both Phase 3 studies used the to-be-marketed formulation (tablet containing 30 mg of micronized ulipristal). The studies providing the majority of safety data in this Application are Phase 3 studies HRA2914-509 and HRA2914-513.

Overall, 4,771 subjects received one or more doses of ulipristal and were studied for safety in the clinical development program. Among the 4,771 subjects, 2,764 (58%) received the to-be-marketed 30 mg ulipristal tablet. In the Phase 3 trials, 84 subjects were enrolled more than once (75 enrolled twice and 9 enrolled three times). Safety analyses were performed on the ITT population (all subjects who received treatment with ulipristal).

Division Director's Comments

- *The size of the safety database is adequate to support approval of ulipristal for the proposed indication.*
- *Additional safety data will be obtained via 4 studies/trials that the Applicant will conduct as postmarketing requirements (see Section 13.4).*

8.2 Deaths and Non-fatal Serious Adverse Events

8.2.1 Deaths

No deaths were reported in the clinical development program.

8.2.2 Nonfatal Serious Adverse Events

Phase 1 studies

Four serious adverse events (SAEs) (bacterial pneumopathy, abdominal pain and fever, Grave's disease, and pilonidal cyst) were reported in the Phase 1 clinical studies; none were considered to be treatment-related by the investigators.

Phase 2 studies

Two SAEs, both in Study HRA2914-507, were reported in ulipristal-treated subjects. One subject had a kidney infection 2 months after ulipristal intake and the second subject had pelvic inflammatory disease approximately one month after ulipristal treatment. Neither SAE was considered by the investigators to be treatment-related.

Phase 3 studies

In Study HRA2914-509, one SAE (seizures with ecstasy use) was reported, but was not considered to be treatment-related.

Seven SAEs were reported during Study HRA2914-513; 3 in the ulipristal treatment group (urinary tract infection, corneal ulcer, and dizziness) and 4 in the LNG treatment group (vomiting blood-stained fluid, molar pregnancy, ruptured ovarian cyst, and kidney stones). Of these, only dizziness (ulipristal group) and molar pregnancy (LNG group) were considered by the investigators to be possibly related to treatment with study drug.

Division Director's Comment

- *No ectopic pregnancies were observed in the clinical trials, although the number of pregnancies was too limited to draw any meaningful conclusions about the risk of ectopic pregnancy if ulipristal is not effective.*

8.3 Discontinuations for Adverse Events

In the Phase 3 studies, 2 ulipristal-treated subjects, both in Study HRA2914-513, discontinued from the study due to an adverse event. One subject vomited within 15 minutes of treatment; the event was considered treatment-related. The second subject had an ovarian cyst that ruptured. According to the investigator's assessment, the event did not fulfill the criteria for an SAE and was not considered treatment-related.

8.4 Common Adverse Events

In the pooled data from the two Phase 3 studies, 56% of subjects who received either ulipristal or LNG reported at least one AE (1,473 of 2,637 ulipristal-treated subjects and 626 of 1,117 LNG-treated subjects). Adverse events reported by ≥ 2% of subjects, regardless of causality, are shown in Table 11. Adverse events reported by at least 5% of subjects were headache, nausea, dysmenorrhea, abdominal pain, fatigue, and dizziness.

Table 11 Common Adverse Events (≥ 2% Subjects) by Preferred Term in the Phase 3 Studies (ITT Population)

Preferred Term	Study HRA2914-509	Study HRA2914-513		Pooled Data (Studies 509+513)
	Ulipristal (N=1,533) n (%)	Ulipristal (N=1,104) n (%)	Levonorgestrel (N=1,117) n (%)	Ulipristal (N=2,637) n (%)
At least one AE	876 (57)	597 (54)	626 (56)	1473 (56)
Headache	269 (18)	213 (19)	211 (19)	482 (18)
Nausea	187 (12)	141 (13)	126 (11)	328 (12)
Dysmenorrhea	102 (7)	142 (13)	160 (14)	244 (9)
Abdominal pain + upper abdominal pain	229 (15)	93 (8)	121 (11)	322 (12)
Fatigue	86 (6)	61 (6)	44 (4)	147 (6)
Dizziness	83 (5)	57 (5)	55 (5)	149 (5)
Nasopharyngitis	41 (3)	31 (3)	32 (3)	72(3)
Back pain	37 (2)	35 (3)	27 (2)	72 (3)
Pelvic pain	59 (4)	0	0	59 (2)
Abdominal distension	32 (2)	17 (2)	14 (1)	49 (2)

Source: Applicant's Summary of Clinical Safety, Adapted from Table 2.7.4-5, pg.19.

Division Director's Comments

- *The nature and frequency of the most common adverse events in the Phase 3 ulipristal treatment groups were similar to those in the LNG treatment group.*

- *The majority of AEs (~90%) were reported as mild or moderate in intensity and resolved spontaneously. Repeat enrollers did not experience AEs more frequently than subjects who enrolled only once.*

8.4.1 Repeat Enrollers

According to the primary Clinical Review, there were 88 women who were repeat enrollers (i.e., subjects who were treated with ulipristal more than once) in efficacy trials (4 in the Phase 2 trials and 84 in Phase 3 trials). Of the 84 (3.2%) subjects who were enrolled in the Phase 3 studies more than once, 75 enrolled twice, and 9 enrolled 3 times. These repeat enrollers did not have an increase in the incidence or severity of AEs. They also did not have (1) an increase in abnormal laboratory parameters, (2) any differences in the duration or volume of menstrual bleeding, and (3) an increase in the incidence of intermenstrual bleeding after taking ulipristal.

8.5 Adverse Events of Particular Interest

Adverse events of special interest after exposure to ulipristal include ovarian cysts, effect on the menstrual cycle, and pregnancy outcomes.

8.5.1 Ovarian Cysts

Three single-dose Phase 1 studies included systematic ultrasonographic evaluation for ovarian cysts (Studies HRA2914-505, -506, and -511). According to the primary Clinical Review, ovarian cysts, ranging from 12 to 52 mm, were observed in all treatment groups, including placebo, and did not appear to be dose-related. All cysts resolved spontaneously except for that in one subject with a persistent 16-mm cyst at 3 months of follow-up.

In the Phase 2 studies, ovarian cysts were reported in both ulipristal groups (10 mg and 50 mg) with equal frequency.

In the Phase 3 studies, one AE of ovarian cyst rupture was reported in each of the ulipristal and LNG treatment groups.

8.5.2 Effect of Treatment on the Menstrual Cycle

The mean increase in menstrual cycle length in subjects who took ulipristal in the Phase 3 trials was 2.5 days, but returned to normal in the subsequent cycle. Seven percent (7%) of subjects reported menses occurring more than 7 days earlier than expected, and 19% reported a delay of more than 7 days. Nine percent (9%) of subjects reported intermenstrual bleeding, but the bleeding was described as spotting in the majority of these subjects.

8.5.3 Pregnancy Outcomes

The Applicant reported, as of June 17, 2010, a total of 113 pregnancies in women exposed to ulipristal in its safety database (92 occurred in the clinical development program and 21 were reported via post-marketing surveillance).

Clinical Trials. Among the 92 pregnancies in the Applicant's clinical development program, 2 occurred in Phase 1, 41 in Phase 2, and 49 in Phase 3 studies. Outcomes for these 92 pregnancies were:

- 60 subjects (65%) had induced pregnancy terminations.
- 15 subjects (16%) had spontaneous abortions.
- 7 subjects (8%) had live births:
 - one infant had optic nerve hypoplasia and developmental delay.
 - 5 infants were reported as normal.
 - One unknown.
- 10 subjects (11%) were lost to follow-up.

Post-Marketing Surveillance. The outcomes of the 21 pregnancies reported in the postmarketing period since approval of ulipristal by the EMA are:

- 14 are ongoing.
- 2 were electively terminated.
- 1 resulted in a spontaneous abortion.
- 4 are unknown.

Division Director's Comments

- *Neither the findings from nonclinical toxicology studies nor the limited clinical findings to date raise any concerns about potential teratogenic effects of ulipristal on an early pregnancy.*
- *To obtain additional information about potential adverse outcomes following exposure to ulipristal, the applicant will be required, as a postmarketing requirement (see Section 13.4), to conduct a prospective, observational pregnancy outcome study to include fetal and neonatal outcomes and maternal pregnancy complications following a pregnancy exposed to ulipristal (e.g., in case of inadvertent administration to a woman with an unrecognized pregnancy or in case of EC failure). This study may be conducted by adding a US component to the Applicant's planned European pregnancy outcome study.*
- *If a signal of concern regarding pregnancy complications is found in the study described above, the Applicant will conduct a follow-up case-control study of pregnancy loss complications as an expansion of the earlier study.*
- *Because it is not known if ulipristal passes into breast milk, the Applicant will be required to conduct a pharmacokinetic trial in lactating women. The trial will evaluate the rate and extent of excretion of ulipristal and its active metabolite into breast milk. Until this information is known, labeling will continue to state: "Use of ella by breastfeeding women is not recommended."*

8.6 Overall Assessment of Safety

The clinical safety database for ulipristal included 4,771 subjects, 2,764 of whom received the to-be-marketed tablet formulation of ulipristal. No deaths occurred and no unexpected adverse outcomes were observed in the clinical development program. The most common adverse reactions were nausea, headache, dysmenorrhea, abdominal pain, fatigue, and dizziness. This profile of common adverse events was very similar to that observed with the approved

emergency contraceptive LNG 1.5 mg. The alterations in menstrual cycle lengths and bleeding volume noted in the Phase 3 trials were well-tolerated and not clinically significant, and do not represent a safety concern. Safety findings from a small number of subjects (n=88) who received ulipristal 2 or 3 times in different menstrual cycles were similar to finding in subjects who received ulipristal only once. Data on pregnancy outcomes after EC failure with ulipristal were too limited to draw any definitive conclusions regarding possible adverse effects of ulipristal on fetal development.

9. ADVISORY COMMITTEE MEETING

This Application was discussed at the Advisory Committee for Reproductive Health Drugs (ACRHD) on June 17, 2010. Among the questions discussed at the Advisory Committee meeting were the following:

1. Has the Applicant provided sufficient information to conclude that ulipristal reduces the likelihood of pregnancy when taken within 120 hours after unprotected intercourse or a known or suspected contraceptive failure?

Yes-11 No-0 Abstain-0

2. Has the Applicant provided sufficient information to conclude that the safety profile for ulipristal is acceptable for the proposed indication?

Yes-11 No-0 Abstain-0

- Committee members commented that additional information regarding information on risk in pregnancy is needed and recommended that this be addressed in the post-approval period.

3. Is there a need for measures beyond product labeling/healthcare provider education to address potential off-label use of ulipristal? If yes, what do you recommend?

Yes-0 No-11 Abstain-0

Other comments/recommendations by the Committee Members included:

- Pregnancy testing would likely be done in practice, with comments noting that this should not be required.
- It was noted that labeling should not recommend use of ulipristal by lactating mothers as data on the possible exposure to ulipristal in breastfed infants are not available.

Division Director's Comments

- *The Committee's assessment of the efficacy and safety of ulipristal strongly supports approval of ulipristal for the prevention of pregnancy when taken within 120 hours after unprotected intercourse or a known or suspected contraceptive failure.*
- *The Committee members recommended that product labeling not require mandatory pregnancy testing prior to prescribing ulipristal.*

10. PEDIATRICS

The Applicant requested a waiver of pediatric studies. The Pediatric Review Committee (PeRC) granted a partial waiver for pre-menarcheal children because they are not at risk for pregnancy. The remainder of the PREA requirement for pediatric studies was fulfilled by extrapolation of data from adults. Clinical experience with a wide variety of hormonal contraceptive products

supports the expectation that the efficacy and safety of ulipristal in postmenarcheal adolescents, like that of other approved hormonal contraceptive products, will not differ significantly from that in adult women. In addition, the Phase 3 clinical trials included 44 adolescents between 16 to <18 years of age.

Division Director's Comment

- *The Applicant will conduct, as a postmarketing requirement (PMR), an observational study in adolescents, with particular focus on alterations of the menstrual cycle after use of ulipristal for EC. The study will likely enroll more than 200 adolescents of which at least 50 subjects should be under the age of 16 years. While safety and efficacy are expected to be the same in adolescents as that demonstrated in adult women, the use of ulipristal by adolescents may result in alterations in the menstrual cycle that differ from those observed in adult women. This is a theoretical possibility because the hypothalamic-pituitary-ovarian axis is more labile in adolescents and may be more vulnerable to disruption by a hormone modulator such as ulipristal.*

11. OTHER RELEVANT REGULATORY ISSUES

Certification of Financial Interests

The Applicant stated in their Application that (1) HRA Pharma has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study, (2) no listed investigator disclosed had a proprietary interest in this product or a significant equity in HRA Pharma, and (3) no listed investigator was a recipient of significant payments from HRA Pharma.

Division of Scientific Investigation Inspections

The clinical investigator sites for 2 Investigators in the US (Dr. William Casale [Study HRA2914-513] and Dr. Savita Ginde [Study HRA 2914-509]) and the Applicant (Laboratoire HRA Pharma) were inspected in support of this NDA. The 2 clinical sites were selected because of their high enrollments.

Casale Site. The DSI inspection identified several subjects that had been enrolled into an incorrect “window treatment group” because of the site’s error in calculating the time window between treatment intake and unprotected intercourse. DSI also noted a few protocol violations concerning inclusion/exclusion criteria. DSI’s overall assessment of this site was “*The review division may wish to consider the impact, if any, of data derived from the subjects noted above. Otherwise, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.*”

Division Director's Comment

- *The FDA statistician reviewed the DSI findings and concluded that the errors in calculating the time window between UPI and treatment intake did not impact the FDA analysis because the FDA statistician independently calculated these time intervals and did not rely on the Applicant’s data in that regard.*

Ginde Site. The DSI inspection did not reveal any significant discrepancies or regulatory violations.

Laboratoire HRA Pharma. The DSI inspection did not reveal any significant discrepancies or regulatory violations.

12. LABELING

The proprietary name of “ella” that was proposed by the Applicant was found to acceptable by the Division of Medication Errors Prevention and Analysis (DMEPA).

The package insert was submitted in the format prescribed by the Physician Labeling Rule (PLR), but initially did not include patient labeling. Upon request by DRUP, the Applicant submitted a Patient Package insert. Review of the package insert (physician and patient labeling) was guided, in part, by the updated draft Guidance for oral contraceptive product labeling, as well as by the approved PLR labels for the levonorgestrel-based EC products (Plan B and Plan B One-Step). Consultative reviews were provided by the Division of Drug Marketing, Advertising and Communication (DDMAC), the Study Endpoints and Label Development (SEALD) team, and the Division of Risk Management (DRISK). Comments from these consultative reviews were incorporated into the label as appropriate.

Major issues addressed in labeling negotiations with the Applicant included:

- Inclusion in Warnings and Precautions section of the need to rule out pregnancy prior to prescribing ulipristal, with use of pregnancy testing if pregnancy could not be excluded by history and/or physical exam.
- Addition of possible effects of ulipristal on the endometrium, along with inhibition of ovulation, as potential mechanisms of action for ulipristal in preventing pregnancy.
- Discussion of the apparent impact of high BMI on reducing the efficacy of both ulipristal and levonorgestrel-based products in preventing pregnancy.

Agreement with the Applicant on final product labeling was reached on August 12, 2010.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

The Applicant has provided sufficient information for me to conclude that ella (ulipristal acetate) tablet will be a safe and effective emergency contraceptive for “prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure” when used in accordance with final agreed-to labeling submitted by the Applicant on August 12, 2010. I therefore recommend that ella (ulipristal acetate) be approved.

13.2 Risk/Benefit Assessment

Findings from two Phase 3 studies demonstrated that treatment with ulipristal administered within 120 hours following unprotected intercourse or a known or suspected contraceptive failure resulted in an observed pregnancy rate that was (1) statistically lower than the expected pregnancy rate in the absence of emergency contraception and (2) lower than the Applicant’s prespecified clinical relevance threshold of 4%. Results of secondary efficacy analyses indicated that ulipristal prevented 60-70% of expected pregnancies. Ulipristal also was shown to be non-inferior to the approved emergency contraceptive levonorgestrel 1.5 mg. No effect of age on the efficacy of ulipristal was observed. The efficacy of ulipristal remained consistent regardless of the time interval between unprotected intercourse and treatment for up to 120 hours after unprotected intercourse. The effectiveness of ulipristal (as well as levonorgestrel for emergency contraception), however, appeared to be reduced in subjects with a BMI > 30 kg/m².

The clinical safety database for ulipristal included 4,771 subjects, 2,764 of whom received the to-be-marketed tablet formulation of ulipristal. No deaths occurred and no unexpected adverse outcomes were observed in the clinical development program. The most common adverse reactions were nausea, headache, dysmenorrhea, abdominal pain, fatigue, and dizziness. This profile of common adverse events was very similar to that observed with the approved emergency contraceptive levonorgestrel 1.5 mg. The alterations in menstrual cycle lengths and bleeding volume noted in the Phase 3 trials were well-tolerated and not clinically significant, and do not represent a safety concern. Safety findings from a small number of subjects (n=88) who received ulipristal 2 or 3 times in different menstrual cycles were similar to finding in subjects who received ulipristal only once.

Data on pregnancy outcomes after failure of ulipristal to prevent a pregnancy were too limited to draw any definitive conclusions regarding possible adverse effects of ulipristal on fetal development. Because of the limitations of preapproval clinical trials, the Applicant will be required to conduct several post approval studies. One of the studies will be a prospective, observational pregnancy outcome study to include fetal and neonatal outcomes and maternal pregnancy complications following a pregnancy exposed to ulipristal (e.g., in case of inadvertent administration to a woman with an unrecognized pregnancy or in case of emergency contraceptive failure).

In summary, ulipristal was effective for prevention of pregnancy when administered within 120 hours following unprotected intercourse or a known or suspected contraceptive failure. The observed safety profile did not raise any concerns and was similar to that of the approved emergency contraceptive levonorgestrel 1.5 mg. The overall risk/benefit profile of ulipristal for emergency contraception is favorable and supports my recommendation for approval.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

No postmarketing risk management activities beyond labeling and the Applicant's standard pharmacovigilance activities are recommended.

13.4 Recommendations for other Postmarketing Requirements and Commitments

Based on the known pharmacology of ulipristal, the Applicant will be required to evaluate further potential risks associated with the use of ulipristal for prevention of pregnancy. This evaluation will require that the Applicant conduct several postmarketing trials or studies because analyses of spontaneous postmarketing adverse event reports are not likely to be adequate to identify (1) unexpected risks of adverse fetal, neonatal, or maternal outcomes following unintended exposure to ulipristal or (2) unexpected adverse events associated with the use of ulipristal by postmenarcheal adolescents, particularly with respect to alterations in their menstrual cycles. It also has been 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. The Applicant will be required to conduct the following studies or trials as postmarketing requirements (PMRs):

1. A prospective, observational pregnancy outcome study to include fetal and neonatal outcomes and maternal pregnancy complications following a pregnancy exposed to ulipristal (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 under No. 1 above) if a signal of concern regarding pregnancy complications is found in Study No. 1.
 3. An observational study in adolescents, with particular focus on alterations to the menstrual cycle after use of ulipristal. 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 under the age of 16 years.
 4. A pharmacokinetic trial in lactating women, with evaluation of the rate and extent of excretion of ulipristal and its active metabolite into breast milk.

In addition to the above PMRs, the Applicant will conduct under a postmarketing commitment (PMC), an *in vivo* drug-drug interaction trial to assess the impact of a CYP3A4 inducer on plasma concentrations of ulipristal. The basis for this commitment is that ulipristal is metabolized by CYP3A4; inducers of CYP3A4 therefore may reduce plasma concentrations of ulipristal, thereby also reducing its effectiveness as an emergency contraceptive.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22474

ORIG-1

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/s/

SCOTT E MONROE
08/13/2010