

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-474

OTHER REVIEW(S)

SEALD LABELING: FINAL SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 022474
APPLICANT	Laboratoire HRA Pharma
DRUG NAME	ella (ulipristal acetate)
SUBMISSION DATE	October 15, 2009
PDUFA DATE	August 15, 2010
SEALD REVIEW DATE	August 12, 2010
OND ASSOCIATE DIRECTOR FOR LABELING OR DESIGNEE	Ann Marie Trentacosti for Laurie Burke

This review confirms that the final draft labeling meets the minimum requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

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/

ANN M TRENTACOSTI
08/12/2010
Signing for Laurie Burke (Associate Director for Labeling)

SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 022474
APPLICANT	Watson Pharma, Inc.
DRUG NAME	ella (ulipristal acetate)
SUBMISSION DATE	October 15, 2009
PDUFA DATE	August 15, 2010
SEALD REVIEW DATE	August 9, 2010
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

Outlined below are the following outstanding labeling issues that must be corrected before the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), "none" is stated. If clearly inapplicable sections are omitted from the FPI, "not applicable" is stated. In addition, "not applicable" is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

Highlights (HL):

- **Highlights Limitation Statement:** None.
- **Product Title Line:** None.
- **Initial U.S. Approval:** None.
- **Boxed Warning:** N/A.
- **Recent Major Changes:** N/A.
- **Indications and Usage:** N/A.
- **Dosage and Administration:** None.
- **Dosage Forms and Strengths:** None.
- **Contraindications:** None.
- **Warnings and Precautions:** None.

SEALD LABELING REVIEW

- **Adverse Reactions:** None.
- **Drug Interactions:** None.
- **Use in Specific Populations:** None.
- **Patient Counseling Information Statement:** None.
- **Revision Date:** The brackets around “8/2010” should be deleted for consistency with other PLRs.

Table of Contents (TOC):

- A horizontal line must be added between the TOC and FPI sections. See 21 CFR 201.57(d)(2).
- There appears to be an extra line between Section 7 and Section 8 headings. Please delete.
- The un-numbered line “Information for Patients” under Section 17 should be deleted as it is no longer a subheading.

Full Prescribing Information:

Boxed Warning: N/A.

1 Indications and Usage: None.

2 Dosage and Administration: None.

3 Dosage Forms and Strengths: None.

4 Contraindications: The section heading referenced in the last sentence in brackets should be changed to lower case: “[See Use in Specific Populations (8.1)]”. See recommended format in “Guidance for Industry: Labeling for Human Prescription Drug and Biological Products --- Implementing the New Content and Format Requirements.”

5 Warnings and Precautions: None.

6 Adverse Reactions: None.

7 Drug Interactions: None.

8 Use in Specific Populations: Section 8.1: The section heading referenced in the brackets should be changed to lower case: “[See Contraindications (4).]”

SEALD LABELING REVIEW

- 9 Drug Abuse and Dependence:** N/A.
- 10 Overdosage:** None.
- 11 Description:** None.
- 12 Clinical Pharmacology:** None.
- 13 Nonclinical Toxicology:** None.
- 14 Clinical Studies:** None.
- 15 References:** N/A.
- 16 How Supplied/Storage and Handling:** None.
- 17 Patient Counseling Information:** None.

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/

JUN YAN
08/09/2010

LAURIE B BURKE
08/09/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****PRE-DECISIONAL AGENCY MEMO*****

Date: August 10, 2010

To: Pam Lucarelli
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A.
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Carrie Newcomer, Pharm.D.
Regulatory Review Officer
DDMAC

Re: **NDA 022474**
DDMAC labeling comments for ELLA (ulipristal acetate) tablet

Background

DDMAC has reviewed the following draft label materials for ELLA (ulipristal acetate) tablet (ella), submitted to DRUP on October 14, 2009:

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer Directed:

- Patient Product Information (PPI)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on August 6, 2010. In addition, we have considered the Plan B approved product labeling (approved July 2009) and Plan B One-Step approved product labeling (approved July 2009) in our review of the draft labeling for ella.

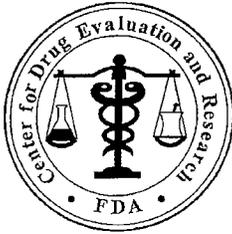
We offer the following comments:

PI & PPI

Please see our attached comments.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
(301) 796-3821, or janice.maniwang@fda.hhs.gov
- Carrie Newcomer (Consumer directed materials)
(301) 796-1233, or carrie.newcomer@fda.hhs.gov



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 2, 2010

To: Scott Monroe, MD
Director, Division of Reproductive and Urologic Products

Through: Solomon Iyasu, MD, MPH
Director, Division of Epidemiology (DEPI)
Office of Surveillance and Epidemiology (OSE)

From: Rita Ouellet-Hellstrom, PhD, MPH
Epidemiologist, Division of Epidemiology (DEPI)
Office of Surveillance and Epidemiology (OSE)

Subject: Observational Study Protocol 2914-010

Drug Name(s): Ella (ulipristal acetate)

Application Type/Number: NDA: 22-474

Applicant/sponsor: HRAPharma /Target Health

OSE RCM #: 2010-1583

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EXECUTIVE SUMMARY

On July 19, 2010, the Division of Reproductive and Urologic Products (DRUP) requested that the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE) review and comment on HRA Pharma/Target Health (the Applicant) draft protocol to evaluate safety, tolerability, and efficacy of ulipristal in postmenarcheal adolescent girls and adult women. As part of approval in the US, DRUP plans to request the Applicant to extend the targeted surveillance to the United States and stratify patients by age (<16 years and ≥ 16 years with approximately 25% of the patients enrolled in the < 16 year old group).

Ulipristal was initially developed by the United States National Institutes of Health and licensed to HRA Pharma in 2000. On May 15, 2009, ulipristal was given marketing approval by the EMEA for the indication of emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure (EU commission decision EU/1/09/522/001 May 15, 2009).

Unfortunately, the limited size and the proposed patient population severely limit the ability of this targeted surveillance to identify and generalize the safety and tolerability in postmenarcheal adolescents and adult women. Consequently, DEPI recommends that

1. Should the proposed targeted surveillance be extended to the US postmenarcheal adolescents and adult women as proposed
 - a. The protocol should be amended to more specifically define the safety issues of concern here (i.e. menorrhagia, metorrhagia, dysmenorrhea, number of days and timing of bleeding with respect to expected period, pregnancy, birth defects) and to specifically include this information as one of the objectives. The populations studied should be more representative of potential users in the US.
 - b. If age grouping is important, recruitment should be targeted for each age group of interest separately using a systematic selection process that is independent of the other age-groups of interest.
 - c. The effort study should be adequately powered to assess the safety concerns delineated in the objectives.
 - d. Important safety and tolerability concerns as stated in the objectives should be captured in a standardized way. The data collection forms could also include sections to capture open-ended comments.
 - e. All demographic and health information including pregnancy and family histories should be collected at baseline and that information on concomitant drugs used be collected at baseline, recorded in the diary and provided to the investigators at each contact with the patient. Collections of information on maternal pregnancy histories should not be restricted solely to those women who become pregnant.
 - f. An aggressive follow-up plan to find the women lost-to follow-up should be initiated.

- g. Concerns about privacy (email) and insurance coverage for medical sequelae should be addressed.
- 2. Since ulipristal's efficacy and safety have not been sufficiently evaluated in postmenarcheal adolescents due to the small number of volunteers and with the expected difficulty in recruiting postmenarcheal adolescents in the US for the adolescent study, a randomized clinical trial evaluating the safety of ulipristal in adolescents could be considered through the Best Pharmaceuticals for Children Act (BPCA) program.

1 BACKGROUND

On July 19, 2010, the Division of Reproductive and Urologic Products (DRUP) requested that the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE) review and comment on HRA/Pharma/Target Health's (the Applicant) draft protocol 2914-010¹ (also referred to as the adolescent study) to evaluate safety, tolerability, and efficacy of ulipristal in postmenarcheal adolescent girls and adult women. As part of approval in the United States (US), DRUP plans to request that the Applicant extend the targeted surveillance to the US and stratify patients by age (<16 years and ≥ 16 years with approximately 25% of the patients enrolled in the < 16 year old group).

Ulipristal acetate is an orally-active selective progesterone receptor modulator (SPRM) characterized by a tissue-specific partial progesterone antagonist effect. Ulipristal acts by modifying the activity of the natural hormone progesterone and is thought to work by stopping the ovaries from releasing an egg and it may also alter the environment in the womb.

Ulipristal was initially developed by the United States National Institutes of Health and licensed to HRA/Pharma in 2000. On May 15, 2009, ulipristal was given marketing approval by the European Medicines Agency (EMA - formerly the EMEA) for the indication of emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure (EU commission decision EU/1/09/522/001 May 15, 2009) for women of reproductive age.

More than 4,000 women have been administered ulipristal during the clinical development program, and no difference in safety or efficacy was detected when results were analyzed by age subgroups. The majority of women enrolled in clinical efficacy trials, however, were between the ages of 18 and 35 years, with only 44 women observed between the ages of 16 and 18 years, none of whom were treated in the US.

Although randomized clinical trials demonstrated efficacy over placebo or comparator drug, there was approximately a 2% breakthrough pregnancy rate. Most pregnancies ended with elective termination or spontaneous abortion but among the known six live births in one trial, one patient delivered a female infant diagnosed with optic nerve hypoplasia. Consequently, maternal bleeding and the safety of the affected fetus and off-label use remains a concern for this product.

As part of ulipristal approval by the EMA, the Applicant committed to addressing safety issues associated with the use of ulipristal by initiating several targeted efforts designed to address pregnancy outcome, use in adolescents, lactation effects, and pregnancy complications in addition to their pharmacovigilance program.

The Applicant is requesting approval in the US for the same indication: oral emergency contraceptive pill to prevent pregnancy up to 120 hours (5 days) after unprotected sex or contraceptive failure in women of reproductive age. Although DRUP is also concerned about several safety questions related to this product (fetal toxicity, lactation, off label

¹ *Prospective Observational Single Arm Open-Label Multicenter Study to Assess Safety, Tolerability and Efficacy of ellaOne[®] (Ulipristal Acetate) for Emergency Contraception in Postmenarcheal Adolescent Girls and Adult Women.*

use, and pregnancy complications), DRUP continues to have concerns about the safety of this product's use by young women and has requested DEPI to review and provide comments on the adolescent protocol submitted to the EMA.

2 MATERIAL REVIEWED

DEPI reviewed the observational study protocol titled *Prospective Observational Single Arm Open-Label Multicenter Study to Assess the Safety, Tolerability and Efficacy of ellaOne® (Ulipristal Acetate) for Emergency Contraception in Postmenarcheal Adolescent Girls and Adult*.

The study is evaluated based on whether the design adequately meets and addresses the proposed study objectives.

3 REVIEW RESULTS

Objectives: The primary and secondary objectives of the proposed study are to assess the safety, tolerability, and breakthrough pregnancy rate in postmenarcheal adolescents and adult women when used for emergency contraception.

Design and Population: The proposed study is a multicenter prospective observation (single arm open-label) of postmenarcheal adolescents (<18 years of age) and adult women (18+ years) presenting for emergency contraception according to the approved indication. After taking ulipristal, women are eligible for the study if they provide consent on site and are willing to provide information on their bleeding, sexual intercourse, concomitant medications, adverse events up to two menstrual cycles and, if applicable, pregnancy outcome.

Sample Size: As agreed with the Paediatric Committee (PDCO) during the PIP procedure for ellaOne® (EMA- 000305-PIP01-08), the target for this study is to enroll 350 patients with at least half (n=175) being adolescent girls. Based on an anticipated 30% lost to follow-up rate, the investigators plan to enroll 500 patients overall (250 in each age group). Recruitment would stop for each age group once 175 unique adolescent or adult patients have completed the study. To balance the number of patients recruited in each age group, each site would recruit 5 minors and 5 adults every 10 patients. Patients would be recruited at 50 different sites in Sweden and UK between May 2010 and April 2011.

Exposure: Eligible women who receive ulipristal acetate (30 mg tablet, single dose) swallowed in front of investigational site staff would be eligible to participate in the study if they meet eligibility criteria. Patients previously enrolled and who completed the initial study are allowed to re-enroll.

Outcome: Menstrual cycle characteristics (resumption and/or changes of cycle length, duration and volume of inter-menstrual bleeding), adverse events (regulatory definition), and breakthrough pregnancy will be assessed. Information would be recorded in a diary for 2 cycles after ulipristal ingestion. Follow-up would be done either by telephone or by email at the patient's convenience for two cycles. The investigator would follow his/her routine procedure for suspected pregnancies and inform HRA Pharmacovigilance department for each patient identified as pregnant. Data on newborn's health would be collected at birth by the HRA Pharmacovigilance.

Statistical analyses: The primary analysis will focus on describing the safety and tolerability of the drug. Descriptive statistics (mean, standard deviation, range minimum-maximum) would be used to summarize outcomes and menstrual characteristics observed for adolescent girls and compared to those of adult women. Pregnancy rates would be calculated for each population and compared using relative risk calculation (and CI 95%).

4 DEPI COMMENTS

Although the proposed “study” is labeled as open-label, it is not a follow-up of patients treated in a randomized clinical trial nor is it a study since there is no hypothesis to test nor a comparator group. This effort, however, can be considered enhanced PharmacoVigilance with prospective clinical follow-up and targeted surveillance of newly treated women. After receiving treatment, consenting women are enrolled and monitored by phone or email for two expected menstrual cycles unless they become pregnant. All pregnancies are entered in the registry.

There are definite strengths to this clinical monitoring design but many more limitations.

4.1 STRENGTHS

This surveillance includes women known to have received the treatment and collects information provided directly to the investigators who, hopefully, record it using standardized formats on forms. Patients record their information in a diary (assumed to be their bleeding experiences and possible pregnancy) and can discuss any concerns with the clinical personnel when contacted. When needed particularly if a pregnancy is suspected, the investigator can perform additional testing based on normal clinical procedures.

4.2 LIMITATIONS

Unfortunately, the data collection format, limited sample size and the proposed patient enrollment protocol may bias the information collected and severely limit the ability to generalize the information to a larger group of postmenarcheal adolescents and adult women users in the community. DRUP would like to request that the study be extended to the US and to include adolescents younger than 16 years of age.

4.2.1 Objectives and Standardized Data Capture

Although the primary and secondary objectives of this targeted surveillance are to assess the safety, tolerability, and breakthrough pregnancy rate in postmenarcheal adolescents and adult women when used for emergency contraception, the objectives are unclear as to which safety and tolerability concerns will be evaluated or monitored. Throughout the protocol, it becomes clearer that information about bleeding, resumption of menstrual cycles and breakthrough pregnancy is of interest but data collection is not standardized (at least standardization is not mentioned in the protocol but was mentioned in the clinical trials supporting the development program) and there is no specific hypothesis to test. Women are asked to record information (assumed to be about bleeding and menses) in a diary. Women would also be contacted by phone or email around the time of their expected menses presumably to assess the return of menses or possible pregnancy.

There are several concerns relating to data capture in this surveillance especially if extended to the US. Although convenient and probably one of the best medium to contact adolescents and young adults is the use of email or texting, use of email to discuss medical information is subject to unwanted intrusion and may be a privacy concern. Email could be used safely to schedule an appointment or to request that the patients telephone the clinic but not to discuss medical information.

The protocol is also unclear whether the information to be recorded in the diary will be pre-specified, open-ended based on patient determination of importance, or a combination of both. If only open-ended information is recorded, the reported events of interest to the investigators may be omitted. Without more specification, the information provided is subject to recall bias.

Although all reported information will be entered on forms or recorded in the diary, the protocol also states that the investigator has the sole responsibility to define whether or not an event is serious and related to treatment. Since there may be 50 different centers, there could be 50 different interpretations of what is serious. Some guidance on how to define these events or review by a panel of experts would provide some comparability across centers.

Finally, the information requested on pregnancy outcome forms differs based on whether the pregnancy is an abortion, a fetal death, or a live birth. Other than event-specific information, maternal and pregnancy history and use of concomitant medications should be obtained for all women under surveillance whether or not a pregnancy occurred. This information would be extremely useful in mounting a study to evaluate potential risk factors that increase the probability of an event.

4.2.2 Sample Size

The investigators plan to recruit 500 patients with the hope of having 175 unique minor and 175 unique adult women complete observation. A 30% loss-to-follow-up rate is also expected. This sample size was agreed to by the Paediatric Committee (PDCO) during the PIP procedure for ulipristal (EMEA- 000305-PIP01-08). The protocol, however, does not provide any additional information on which criteria were used to calculate the sample size and which adverse event is of primary concern. Given the small number of women in each age group, any safety issue identified would likely raise a serious concern. Because of the limited size of the population under surveillance, the absence of any observed adverse events (particularly congenital malformations²) does not necessarily translate into concluding it is a safe drug but rather that none have been observed in the study population.

The expected 30% loss to follow-up is also a major concern since it is highly likely that these women could have experienced an adverse event and sought care from their medical provider rather than the investigator at the study center. An aggressive follow-up should be contemplated.

² Assuming 350 women complete the study with 2% breakthrough pregnancies, we would expect only 7 live births. No congenital anomaly would be expected even with a most generous population rate of 1 per 200 live births.

4.2.3 Generalizability

There is no randomization or comparator population proposed for this study.

Although the selection criteria in this protocol imply a systematic sampling of patients, to balance the number of patients recruited in each population, the centers are requested to recruit 5 minors and 5 adults every 10 patients. Systematic selection will fail if too many qualified adults are not recruited to meet recruitment requirement of minors. It is also unknown but unlikely that selection of the treatment centers will be randomized.

Consequently, results from the study would be applicable only to the women recruited who complete the study rather than to the more generalized population treated with ulipristal. DEPI recommends that, if the study is extended to the US and age grouping is important, recruitment should be targeted for each age group of interest separately using a systematic selection process that is independent of the recruitment in the other age-groups of interest.

Finally, the protocol states that patients who complete the study would also be allowed to re-enroll. Over 10% were repeaters in the program development phase. A significant number of repeaters would bias the study results in favor of the drug since only those women for whom the treatment is effective and who have not experienced serious adverse events would likely be repeaters. DEPI recommends that if repeaters are allowed, only the first occurrence be considered to satisfy the recruiting quota although information on repeaters could be captured to characterize this group.

4.2.4 Postmenarcheal Adolescents

The program development studies supporting the application demonstrated that recruiting postmenarcheal adolescents in Europe is difficult (only 44 of 1,533 women in the UK). If this is a problem in the UK and Sweden where medical coverage is readily available, recruitment would definitely be a major problem for this age-group in the US where most states require parental consent or at least parental notification for treatment. It is not known from the clinical trials whether adult women are more likely to consent than postmenarcheal adolescents of reproductive age or whether there are more adult women presenting to the clinics. Without intruding on privacy, the clinical centers could keep a log on the number of women offered participation and the number of those who accept by age group and provide a summary at the end of observation.

In addition, with the current medical insurance rules in the US, any complications resulting from treatment might be deemed a pre-existing condition and not be eligible for reimbursement, possibly jeopardizing needed medical care. Consenting adults may or may not be aware of this problem but it is highly likely postmenarcheal adolescents would not know. This could present a medical care problem unless the clinical centers take responsibility for treatment as well.

Since ulipristal's efficacy and safety have not been sufficiently evaluated in postmenarcheal adolescents due to the small number of volunteers and with the expected difficulty in recruiting postmenarcheal adolescents in the US, a randomized clinical trial evaluating the safety of ulipristal in adolescents could be considered through the Best Pharmaceuticals for Children Act (BPCA) program.

5 RECOMMENDATIONS

Unfortunately, the limited size and the proposed patient population severely limit the ability of this targeted surveillance to identify and generalize the safety and tolerability in postmenarcheal adolescents and adult women. Consequently, DEPI recommends that

1. Should the proposed targeted surveillance be extended to the US postmenarcheal adolescents and adult women as proposed
 - a. The protocol should be amended to more specifically define the safety issues of concern here (i.e. menorrhagia, metorrhagia, dysmenorrhea, number of days and timing of bleeding with respect to expected period, pregnancy, birth defects) and to specifically include this information as one of the objectives. The populations observed should be more representative of potential users in the US.
 - b. If age grouping is important, recruitment should be targeted for each age group of interest separately using a systematic selection process that is independent of the other age-groups of interest.
 - c. The effort be adequately powered to assess the safety concerns delineated in the objectives.
 - d. Important safety and tolerability concerns as stated in the objectives should be captured in a standardized way. The data collection forms could also include sections to capture open-ended comments.
 - e. All demographic and health information including pregnancy and family histories should be collected at baseline and that information on concomitant drugs used be collected at baseline, recorded in the diary and provided to the investigators at each contact with the patient. Collections of information on maternal pregnancy histories should not be restricted solely to those women who become pregnant.
 - f. An aggressive follow-up plan to find the women lost-to follow-up should be initiated.
 - g. Concerns about privacy (email) and insurance coverage for medical sequelae should be addressed.
2. Since ulipristal's efficacy and safety have not been sufficiently evaluated in postmenarcheal adolescents due to the small number of volunteers and with the expected difficulty in recruiting postmenarcheal adolescents in the US for the adolescent study, a randomized clinical trial evaluating the safety of ulipristal in adolescents could be considered through the Best Pharmaceuticals for Children Act (BPCA) program.

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/

RITA P OUELLET-HELLSTROM
08/02/2010

SOLOMON IYASU
08/02/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 27, 2010
To: Scott Monroe, M.D., Division Director
Division of Reproductive and Urologic Products (DRUP)
Through: Mary Willy, PhD, Deputy Director
Division of Risk Management (DRISK)
LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management
From: Melissa Hulett, MSBA, BSN, RN
Patient Product Information Reviewer
Division of Risk Management
Subject: DRISK Review of Patient Labeling (Patient Product Information)
Drug Name(s): ella (ulipristal acetate)
Application Type/Number: NDA 22-474
Applicant/sponsor: Laboratoire HRA Pharma
OSE RCM #: 2010-1444

1 INTRODUCTION

Laboratoire HRA Pharma submitted an original 505 (b) (1) New Drug Application, NDA 22-474, ella (ulipristal acetate) tablet, on October 14, 2009. Ella (ulipristal acetate) is emergency contraception indicated for the prevention of pregnancy following unprotected intercourse or known or suspected contraceptive failure.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Product Information (PPI) for ella (ulipristal acetate). Please let us know if DRUP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft ella (ulipristal acetate) Prescribing Information (PI) received on October 15, 2009 and revised by the Review Division throughout the current review cycle and received by DRISK on July 2, 2010.
- Draft ella (ulipristal acetate) Patient Product Information (PPI) received on October 15, 2009 and received by DRISK on July 2, 2010.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the Regulations as specified in 21 CFR 208.20
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

14 Page(s) of Draft Labeling have been withheld in full immediately following this page as B4 (CCI/TS)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 07, 2010

To: Scott Monroe, MD, Director
Division of Reproductive and Urology Products

Through: Carlos M Mena-Grillasca, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Walter Fava, R.Ph., MSED., Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Ella (Ulipristal Acetate) Tablet
30 mg

Application Type/Number: NDA 022474

Applicant: Target Health Inc., for Laboratoire HRA Pharma

OSE RCM #: 2009-2169-1

1 INTRODUCTION

This review responds to a request from the Division of Reproductive and Urology Products for a review of the revised Ella labels and labeling in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA provided label and labeling recommendations under OSE Review # 2009-2169 dated March 18, 2010.

2 MATERIAL REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the revised labels and labeling submitted by the Applicant on May 14, 2010 (Appendix A and B). We also evaluated the recommendations in OSE review #2009-2169.

3 CONCLUSION

The Applicant has satisfactorily revised the labels and labeling per our previous review. They have addressed all of our concerns thus, we have no further comments.

If you have questions or need clarifications, please contact Maria Wasilik, OSE Project Manager, at (301) 796-0567.

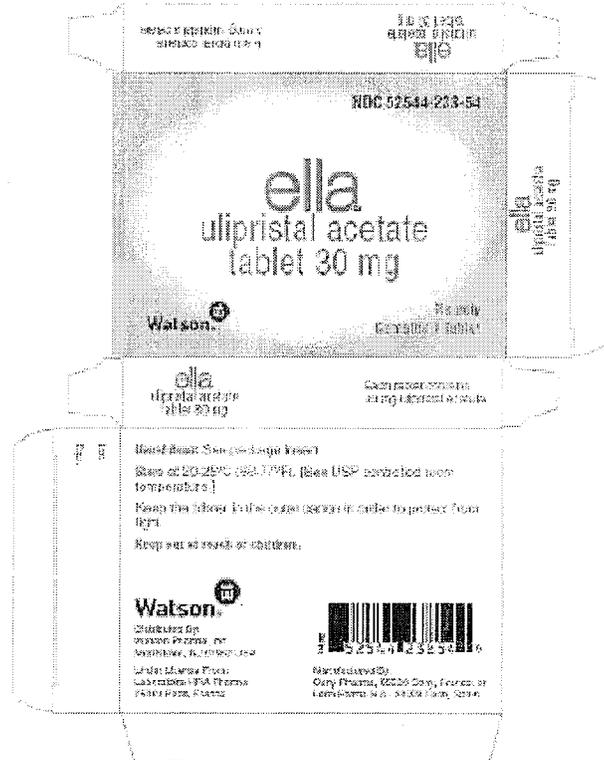
¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

4 APPENDICES

APPENDIX A: Unit dose blister label



APPENDIX B: Carton labeling



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/

WALTER L FAVA
07/07/2010

CARLOS M MENA-GRILLASCA
07/07/2010

DENISE P TOYER
07/09/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 18, 2010

To: Scott Monroe, MD, Director
Division of Reproductive and Urologic Products

Through: Carlos M Mena-Grillasca, R.Ph., Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Walter Fava, RPh, MSED, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Labels and Labeling Review

Drug Name(s): Ella (Ulipristal Acetate) Tablets
30 mg

Application Type/Number: NDA 022474

Applicant: Target Health Inc., for Laboratoire HRA Pharma

OSE RCM #: 2009-2169

1 INTRODUCTION

This review is written in response to a request from the Division of Reproductive and Urologic Products for assessment of labels and labeling for Ella (Ulipristal Acetate) Tablets, 30 mg, for their vulnerability to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the labels and labeling submitted on January 19, 2010 (see Appendix A).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the blister label, carton and package insert labeling can be improved to minimize the potential for confusion that may contribute to medication errors. We provide recommendations on the insert labeling in Section 3.1 Comments to the Division for discussion during the label and labeling meetings. We provide our recommendations for the blister labels and carton labeling in Section 3.2, Comments to the Applicant, below. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Maria Wasilik, OSE Regulatory Project manager, at 301-796-0567.

3.1 COMMENTS TO THE DIVISION

Our evaluation of the package insert labeling noted the following areas where presentation of information could be revised to provide clarity:

In section 17, 'Patient Counseling Information', revise the following to be consistent with other sections of the insert labeling:

- a. Revise the statement, '...than 120 hours after unprotected intercourse...', to read, '...than 120 hours (**5 days**) after unprotected intercourse...'. Note the addition of '(5 days)'.
- b. Add the statement, 'Tablet can be taken with or without food'.

3.2 COMMENTS TO THE APPLICANT

A. Blister Labels

1. Ensure that the presentation of the established name is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

2. Revise the presentation of the proprietary name, established name, dosage form, and strength statements on the blister label to appear in the following sequence:

ella

Ulipristal Acetate Tablet

30 mg

3. Increase the prominence of the strength statement. As currently presented, it is small and difficult to read.
4. Ensure the expiration date and lot number are included on the label to be in accordance with 21 CFR 201.17.
5. Provide instructions for opening the blister package to ensure safe removal of the tablet. It is unclear whether patients are to push the tablet through the foil backing or if they are suppose to peel back the printed side of the blister to remove the tablet. We recommend deleting the Watson graphic to allow room for this information.

B. Carton Labeling

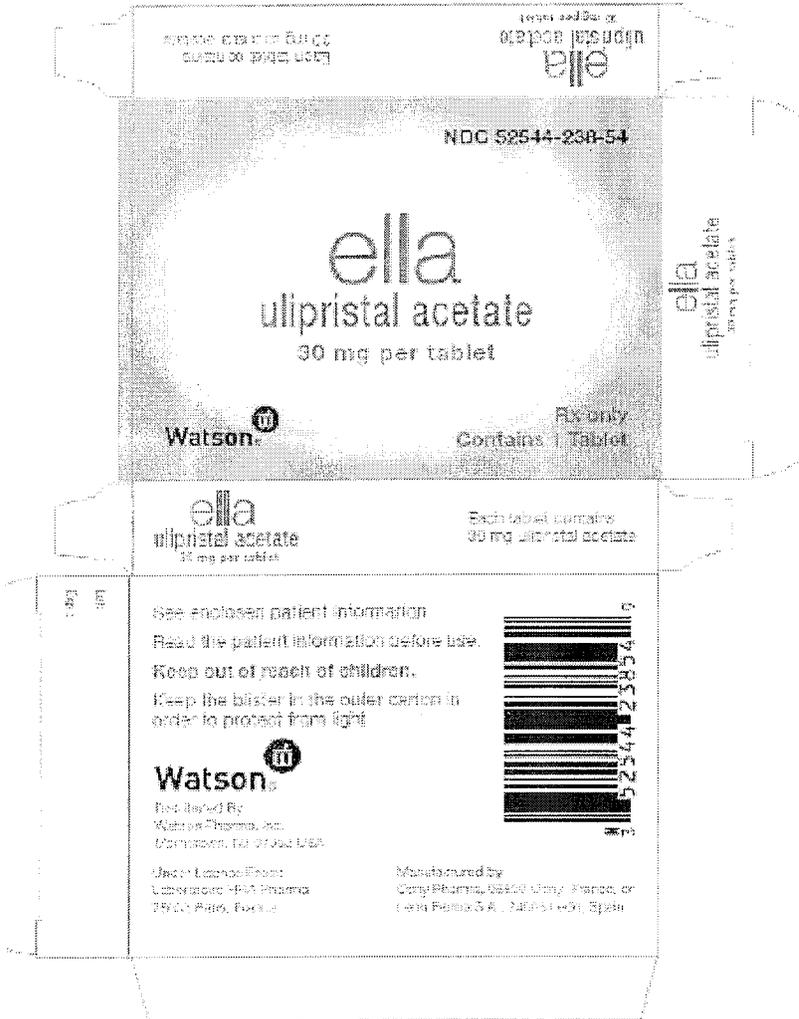
1. Ensure that the presentation of the established name is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. Include the dosage form statement immediately following the established name.
3. Increase the size of the strength statement, '30 mg per tablet'.
4. Revise the statement, 'See enclosed patient information' to include, 'Usual Dose: See Package Insert' or 'Usual Dose: One tablet, 30 mg, one time dose', in accordance with 21 CFR 201.55. As currently presented, the dosing statement is not clearly stated.

3.2.1 APPENDICES

Appendix A: Unit dose blister label



Carton Labeling



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/

WALTER L FAVA
03/18/2010

CARLOS M MENA-GRILLASCA
03/18/2010

DENISE P TOYER
03/18/2010

CAROL A HOLQUIST
03/18/2010

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 - Animal Efficacy Rule
 - Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a long-term, prospective observational study of women who use ulipristal for emergency contraception, yet still become pregnant (e.g., via an unrecognized pregnancy existing at the time of dosing, or because of emergency contraceptive failure). This study may be conducted by adding a US component to the Applicant's planned European pregnancy outcome study.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

Primary safety study or clinical trial

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Long-term safety study
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

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/

PAMELA LUCARELLI
08/13/2010

AUDREY L GASSMAN
08/13/2010

PMR/PMC Development Template – PMR #2

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: A case-control study of pregnancy loss complications that will be conducted if a signal of concern regarding pregnancy complications is identified in PMR 1673-1.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 02/13/2011
Study/Clinical trial Completion Date: 12/31/2014
Final Report Submission Date: 06/30/2015
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Although there is no safety signal from the completed phase 3 trials, more pregnancy outcome data may be needed regarding the effects of ulipristal. It will take several years to accrue a sufficient number of women in Study 1673-1 who become pregnant to determine if Study 1673-2 is necessary. Therefore, this study is more appropriate as a postmarketing study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is obtain more safety information regarding whether exposure to ulipristal early in pregnancy is associated with pregnancy loss or adverse maternal outcomes.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR is a required case-control study of women who experience pregnancy loss and/or adverse maternal outcomes after exposure to ulipristal in early pregnancy (e.g., via an unrecognized pregnancy existing at the time of dosing, or because of emergency contraceptive failure). It will be required only if a signal for increased risk of pregnancy loss and/or adverse maternal outcomes is detected in PMR study 1673-1.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
 - This study will only be required if a signal for increased risk of pregnancy loss and/or adverse maternal outcomes is detected in PMR study 1673-1.

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

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/

PAMELA LUCARELLI
08/13/2010

AUDREY L GASSMAN
08/13/2010

PMR/PMC Development Template – PMR #3

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: 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 your 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).

PMR/PMC Schedule Milestones: Final protocol Submission Date: 02/13/2011
Study/Clinical trial Completion Date: 04/30/2012
Final Report Submission Date: 10/30/2012
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Although there is no safety signal from the completed phase 3 trials, more data are needed regarding the effects on the menstrual cycle of ulipristal used by adolescent women. This study will evaluate whether the effects of ulipristal on menses are similar in women who have recently attained menarche as compared to older, regularly cycling women.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is obtain additional safety information regarding the effect of ulipristal in adolescent women, with particular focus on the effect on the menstrual cycle.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR is a required observational clinical study in adolescent women who use ulipristal for emergency contraception.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Deputy Director for Safety, Division of Reproductive and
Urologic Products

(signature line for BLAs)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22474	ORIG-1	LABORATOIRE HRA PHARMA	Ella , Ulipristal Acetate

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PAMELA LUCARELLI
08/13/2010

AUDREY L GASSMAN
08/13/2010

PMR/PMC Development Template – PMR #4

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 10/13/2010
Study/Clinical trial Completion Date: 10/13/2011
Final Report Submission Date: 04/30/2012
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Lactating women were excluded from participation in the clinical trials of ulipristal, so there are no data on whether ulipristal is excreted into breast milk. Currently, ulipristal is not recommended for use by breastfeeding women; data from this study may provide more information to be included in labeling.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this clinical trial is to evaluate the extent to which ulipristal and its active metabolite are excreted into breast milk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR is a required clinical trial to gain more information regarding the excretion of ulipristal into breast milk. The Applicant's planned lactation trial to be conducted in Chile appears likely to fulfill this requirement.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

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/s/

PAMELA LUCARELLI
08/13/2010

AUDREY L GASSMAN
08/13/2010

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMC is a clinical drug interaction (between uriliprsital acetate and CYP3A4 inducer) trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

In vivo drug-drug interaction trial

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Deputy Director for Safety, Division of Reproductive and Urologic Products

(signature line for BLAs)

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PAMELA LUCARELLI
08/13/2010

AUDREY L GASSMAN
08/13/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 10, 2010

TO: Pamela Lucarelli, Regulatory Project Manager
Ron Orleans, M.D., Medical Officer
Division of Reproductive and Urologic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-474

APPLICANT: Laboratoire HRA Pharma

DRUG: Ella (ulipristal acetate)

NME: Yes

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Prevention of pregnancy following unprotected intercourse or a known
or suspected contraceptive failure

CONSULTATION
REQUEST DATE: December 17, 2009

DIVISION ACTION
GOAL DATE: August 13, 2010

PDUFA DATE: August 15, 2010

I. BACKGROUND:

The sponsor submitted this NDA for the use of ulipristal acetate in providing emergency contraception. Two pivotal studies, Protocols 2914-004 and 2914-005 were submitted in support of the application.

The conduct of Protocols 2914-004 and 2914-005 entitled "A Prospective, Randomized, Single Blind, Multicenter Study to Compare the Efficacy, Safety and Tolerability of CDB-2914 with Levonorgestrel as Emergency Contraception Within 120 Hours of Unprotected Intercourse", and "A Prospective, Open-Label, Single Arm, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of CBD-2914 as Emergency Contraception When Taken Between 48 Hours and 120 Hours of Unprotected Intercourse", respectively, was inspected.

Protocol 2914-004 was designed as a prospective, single-blind, multicenter, randomized, 2-armed parallel groups (1:1) study. The primary objective of this study was to demonstrate that the pregnancy rate observed after taking 30 mg of CDB-2914 within 72 hours of unprotected intercourse was statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception. The primary efficacy endpoint was the pregnancy rate calculated as the number of subjects being pregnant after the intake of emergency contraception, divided by the number of subjects having received emergency contraception.

Protocol 2914-005 was designed as a prospective open-label, multicenter study. The primary objective of this study was to demonstrate that the pregnancy rate observed after taking 30 mg of CDB-2914 between 48 hours and 120 hours of unprotected intercourse was statistically significantly lower than the estimated expected pregnancy rate in the absence of emergency contraception. The primary efficacy parameter was the pregnancy rate calculated as the number of pregnancies after the intake of emergency contraception, divided by the number of subjects having received emergency contraception.

Note that Protocols 2914-004 and 2914-005 were similar in design but not identical.

Two domestic clinical investigators and the sponsor were selected for inspection. The clinical sites were selected for inspection because of their high enrollments.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site #42 Dr. William Casale Planned Parenthood of Greater Miami Palm Beach and Treasure Coast 11440 SW 88th Street, # 109 Miami, FL 33176 786-263-0001	2914-004/ 180 (enrolled)/	3-7 Mar 2010	VAI
Site #39 Dr. William Casale Planned Parenthood of Greater Miami Palm Beach and Treasure Coast 801 Village Boulevard, Suite 304 West Palm Beach, FL 33409 561-683-0302	2914-004/ 112 (enrolled)/	3-7 Mar 2010	VAI
Site #7 Dr. Savita Ginde 921 E 14th Avenue Denver, CO 80218 303-832-5069	2914-005/ 116 (screened)/	9-11 Mar 2010	NAI.
Site #9 Dr. Savita Ginde 131 W County Line Road Littleton, CO 80129 303-798-0963	2914-005/ 148 (screened)/	9-11 Mar 2010	NAI.
Laboratoire HRA Pharma (Sponsor) 15, rue Béranger, F-75003 Paris France +33 (0) 1 40 33 11 30	2914-004 and 2914-005/	29 Mar-2 Apr 2010	Pending. Interim classification NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

Note: Two clinical investigators were inspected; however, each conducted the study at two separate sites. The conduct of the study by each investigator is summarized separately by site below.

1. Site # 42

Dr. William Casale
Planned Parenthood of Greater Miami
Palm Beach and Treasure Coast
11440 SW 88th Street, # 109
Miami, FL 33176

- a. **What was inspected:** At this site, 180 subjects were enrolled with 170 completing the study. The records of 60 subjects were audited. The audit covered, but was not limited to, informed consent forms, corresponding source documents, IRB and sponsor correspondence, drug accountability records, and monitoring visit records.
- b. **General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Inspection revealed that Subjects 005 and 007 were randomized to treatment despite having unprotected intercourse more than 120 hours prior to requesting emergency contraception. In addition, Subjects 003, 004, 008, 011, 026, 116, and 124 were enrolled in the wrong window treatment group because of the site's error in calculating the time window between treatment intake and unprotected intercourse (within 72 hours and between 72-120 hours). According to a May 6, 2010, memo from the sponsor, these subjects that were improperly randomized to the wrong window treatment group were excluded from the Per Protocol analysis.
- c. **Assessment of data integrity:** 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.

2. Site # 39

Dr. William Casale
Planned Parenthood of Greater Miami
Palm Beach and Treasure Coast
801 Village Boulevard, Suite 304
West Palm Beach, FL 33409

- a. **What was inspected:** At this site, 112 subjects were enrolled with 99 completing the study. The records of 40 subjects were audited. The audit covered, but was not limited to, informed consent forms, corresponding source documents, IRB and sponsor correspondence, drug accountability records, and monitoring visit records.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
 - c. Assessment of data integrity:** Data appear acceptable in support of the respective application.
- 5. Laboratoire HRA Pharma (Sponsor)
15, rue Béranger,
F-75003 Paris
France
 - a. What was inspected:** The sponsor's study activities with regard to, but not limited to, organization and personnel, selection and monitoring of clinical investigators and monitors, quality assurance, adverse event reporting, automated data entry, and test article accountability were evaluated.
 - b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
 - c. Assessment of data integrity:** Data appear acceptable in support of the respective application.

Note: The observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Casale and Ginde and the sponsor, Laboratoire HRA Pharma, were inspected in support of this NDA. Each investigator conducted his or her study at two different sites which comprised a single inspection, and a single regulatory letter was issued to each investigator based on the overall findings of the inspection. Although regulatory violations were noted at Dr. Casale's sites, the findings are unlikely to impact data integrity as those subjects improperly randomized to the wrong window treatment group were excluded from the Per Protocol analysis according to the sponsor. The study appears to have been conducted adequately, and the data generated by the clinical sites of Drs. Casale and Ginde appear acceptable in support of the respective indication.

The inspection of the sponsor noted no significant regulatory violations.

Note: The final classification of the sponsor inspection is pending receipt and review of the EIR. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR.

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22474

ORIG-1

LABORATOIRE
HRA PHARMA

Ella , Ulipristal Acetate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROY A BLAY
06/11/2010

TEJASHRI S PUROHIT-SHETH
06/11/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22474	ORIG-1	LABORATOIRE HRA PHARMA	Ella , Ulipristal Acetate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MELISSA I HULETT
07/27/2010

MARY E WILLY
07/28/2010
I concur

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022474 BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: ulipristal acetate Dosage Form: tablets Strengths: 30 mg		
Applicant: Laboratoire HRA Pharma Agent for Applicant (if applicable): Target Health		
Date of Application: October 14, 2009 Date of Receipt: October 15, 2009 Date clock started after UN:		
PDUFA Goal Date: August 15, 2010	Action Goal Date (if different): August 13, 2010	
Filing Date: November 29, 2009	Date of Filing Meeting: November 24, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Emergency contraceptive indicated for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 049381				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required Note: User fee paid, prior to approval of small business waiver			
 <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b)</i>				

applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the orphan designation at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the orphan designation at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm		X																		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance¹? If not, explain (e.g., waiver granted).</p>	X			
Index: Does the submission contain an accurate comprehensive index?	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	X			
<p>Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p>			X	
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>		X		MedGuide may be needed for this product
REMS consulted to OSE/DRISK?		X		REMS may be needed for this product
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				

<i>If no, request in 74-day letter.</i>				
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Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): April 19, 2004	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 12, 2008	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): July 25, 2006	X			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 24, 2009

BLA/NDA/Supp #: NDA 022474

ESTABLISHED/PROPER NAME: ulipristal acetate

DOSAGE FORM/STRENGTH: 30 mg tablet

APPLICANT: Laboratoire HRA Pharma /Target Health

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Emergency contraception indicated for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

BACKGROUND: Ulipristal acetate is being developed as an emergency contraceptive to be taken within 120 hours of unprotected intercourse. Ulipristal acetate is a progesterone receptor modulator that reversibly blocks the progesterone receptors in target tissues. It belongs to the class of Selective Progesterone Receptor Modulators (SPRM).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pam Lucarelli	Y
	CPMS/TL:	Jennifer Mercier	Y
Cross-Discipline Team Leader (CDTL)	Lisa Soule		Y
Clinical	Reviewer:	Ron Orleans	Y
	TL:	Lisa Soule	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Hyunjin Kim	N
	TL:	Myong-Jin Kim	N
Biostatistics	Reviewer:	Sonia Castillo	Y
	TL:	Mahboob Sobhan	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jeffery Bray	Y
	TL:	Alex Jordan	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Bogdan Kurtyka	Y
	TL:	Moo-Jhong Rhee Donna Christner - PAL	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers	Walter Fava	Y
Other reviewers	Tapash Ghosh	Y
Other reviewers	Rafael Arroyo	Y
Other reviewers	Scott Monroe	Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p>CMC Labeling Review (BLAs/BLA supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
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REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, Office Director	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22474

ORIG-1

LABORATOIRE
HRA PHARMA

Ella , Ulipristal Acetate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PAMELA LUCARELLI
12/10/2009

JENNIFER L MERCIER
12/10/2009