

June 2, 2010

Via Electronic Delivery

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Comment to Docket No. FDA-2010-N-0001
Advisory Committee for Reproductive Health Drugs; Notice of Meeting
Ulipristal acetate tablets, (NDA) 22-474, Laboratoire HRA Pharma.

To Whom It May Concern:

Acting pursuant to a Notice of Meeting published in the Federal Register by the Food and Drug Administration (“FDA”),¹ the American Association of Pro Life Obstetricians & Gynecologists (“AAPLOG”) hereby submits these comments to Docket No. FDA-2010-N-0001 regarding the proposed approval of ulipristal acetate (“ulipristal”) tablets (NDA 22-474) for use as a post-coital contraceptive.²

AAPLOG is a non-profit organization that is greatly concerned with all medical issues related women’s reproductive health – particularly those which endanger the lives of pre-born human beings. Since fertilization marks the beginning of human life, AAPLOG supports the protection of unborn human beings from fertilization to birth. It is a recognized interest group of the American College of Obstetricians and Gynecologists (“ACOG”), currently representing over 2,000 obstetricians and gynecologists throughout the United States of America.

AAPLOG believes that NDA 22-274 *should not be approved* for the reasons described below. In summary, AAPLOG has concluded from publicly available information that ulipristal acetate is an abortifacient of the same type as mifepristone (“RU-486”) and that its approval as an emergency contraceptive raises serious health and ethical issues. Furthermore, ulipristal’s potential effects on women who used the drug off-label and upon ongoing pregnancies are essentially unexamined and untested.

Ulipristal’s ability to destroy established pregnancies, as well as prevent implantation, makes it an embryocidal drug. If FDA were to approve NDA 22-274 without making clear to the public that ulipristal has a substantial abortifacient capability – that action would violate the public trust granted FDA by Congress. Ulipristal’s abortifacient mechanisms require that any approval occur with significant distribution restrictions and heightened notice to potential users.

I. FDA’s Actions Related to this Public Meeting and Comment Submission Have Been Non-Transparent

AAPLOG is extremely disappointed in the non-transparent manner in which this hearing and associated activities have been handled by FDA. We take note of the importance of advisory committees in the FDA decision-making process. For example, we are aware of recent remarks by FDA Commissioner, Dr. Margaret A. Hamburg, who wrote in a letter to her colleagues:

FDA is advised by 49 committees and panels with more than 600 members. These committees provide advice on specific regulatory decisions, such as product approvals, and general policy matters, such as regulations and guidance.³

Dr. Hamburg went on to say that “[t]he primary goal of the advisory committee process is to bring high-quality input to FDA in order to support agency decisions.”

It would be impossible for any reasonable observer to believe that FDA’s process with regard to the upcoming advisory committee hearing or the filing of comments has been remotely transparent or designed to “bring high-quality input to FDA in order to support agency decisions.”⁴ Our primary objection is that these comments were required to be filed before background materials on the NDA have been released to the public. If the prospect of releasing an abortifacient on the market as a contraceptive were not so serious, the agency’s process would be merely puzzling. How can one produce high-quality comments designed to inform the agency when the relevant materials have not been released to the public? When only proponents of the NDA have important knowledge about the process – something is amiss. Similarly, speakers at the public hearing have been required to submit their powerpoint presentations by June 7, and, to date, the supporting documents for the NDA have not been made public.

Clearly, the notice-comment model used in rulemakings should be employed in instances like this. The materials needed for analyzing the NDA should be release by FDA and then some period of time, on the order of 30 or 60 days, should be given to write and file comments. The public hearing should follow after all the comments are made available to the public. Furthermore, the background materials must include all adverse event reports produced in the trials related to the NDA application and FDA documents, including but not limited to, the agency’s review documents written by its staff (*e.g.*, the medical officer’s review, the statistical reviewer’s analysis, etc.).⁵

II. Ulipristal's Mode of Action Includes Embryo Toxicity that Requires a Black Box Warning, Mandatory Pregnancy Registry and Counseling to Satisfy Informed Consent

A. Ulipristal Acts as An Abortifacient and Pregnant Women Will Take the Drug

There is no doubt that ulipristal acts as an abortifacient because the drug blocks progesterone receptors at three critical areas. These blocking capabilities form the basis of its embryocidal-abortifacient mechanism. That mechanism is identical to the action of RU-486 in early pregnancy. This should not be surprising because ulipristal is a "selective progesterone receptor modulator" ("SPRM") very closely related chemically to the FDA-approved abortifacient RU-486. An SPRM acts primarily by blocking progesterone receptors throughout the body.

This receptor blockade interferes with the hormone action of progesterone to prepare the endometrium for implantation and to support the early pregnancy. As the European Medicines Agency ("EMA") noted, "Ulipristal acetate prevents progesterone from occupying its receptor, thus the gene transcription normally turned on by progesterone is blocked, and the proteins necessary to begin and maintain pregnancy are not synthesized."⁶ This has an endometrial effect described by the EMA as follows: "*In vivo* pharmacology results show that ulipristal acetate has antiprogestosterone activity shown as inhibition of progesterone induced endometrial glandular proliferation...."⁷ The EMA also made this observation regarding ulipristal's toxicity on pregnancies in various animal species, "Due to its mechanism of action, ulipristal acetate has an embryolethal effect in rats, rabbits (at repeated doses above 1 mg/kg) and in monkeys."⁸

Ulipristal has three embryocidal modes of action all of which involve blocking progesterone:

1. Ulipristal blocks progesterone at the level of the endometrial glands, and destroys the receptivity of the endometrium so that the embryo cannot implant;⁹
2. Ulipristal destroys the capacity of the corpus luteum granulosa cells to produce progesterone; production of progesterone at the corpus luteum level supports the implanted embryo throughout the first 10 weeks of pregnancy; absent this corpus luteal progesterone production, the placenta which feeds the embryo will die; this mechanism of action is identical to the action of RU-486 on the corpus luteum;¹⁰
3. Ulipristal directly blocks progesterone receptors in the endometrial stromal tissue, identical to the mechanism of action of mifepristone (RU-486) which kills the implanted embryo by directly destroying the maternal component of the placenta.¹¹

This embryocidal mechanism of action distinguishes ulipristal from Levonorgestrel (Plan B). Levonorgestrel does not disrupt a pregnancy which has already implanted.¹² Given the information provided above, it is inevitable that ulipristal will abort established uterine pregnancies when used in real world situations.¹³

According to the EMEA, “Ellaone is contra-indicated during an existing or suspected pregnancy.”¹⁴ Yet, in clinical use as an emergency contraceptive, ulipristal use in pregnant women cannot be avoided, for three reasons:

1. Known treatment failure with Ulipristal is approximately 2% (2.1% in Fine et al.,¹⁵ 0.9% in Creinin et al.,¹⁶ and 1.8% in Glasier et al.¹⁷). Thus of every 100 women who take Ulipristal, approximately two will continue a pregnancy now exposed to Ulipristal.
2. In all phase III trials ulipristal was administered to women who were later judged to been pregnant prior to administration (one pregnancy in Fine et al.,¹⁸ four pregnancies in Creinin et al.,¹⁹ four pregnancies in Glasier et al.,²⁰). So even under the best circumstances of a clinical trial, preexisting pregnancy could not be excluded. The numbers from Fine, Creinin and Glasier undoubtedly underestimate the true preexisting pregnancy rate, because ulipristal itself is an abortifacient, and the numbers given in the trials only represent those embryos who survived the Ulipristal treatment. Also the lack of data for an average of 7.2% of patients underestimates the true number of those administered ulipristal during pregnancy and those who have continued pregnancy after ulipristal exposure. Incomplete data and/or dropouts (lost to follow-up) includes 106/1241 (8.5%) in Fine et al.,²¹ 94/1578 (6%) in Creinin et al.,²² and 134/1899 (7%) in Glasier et al.²³
3. The long half life of ulipristal²⁴ (in monkeys drug detected in all investigated tissues up to 14 days after single dose)²⁵ which extends beyond the 5 day window of treatment efficacy means that Ulipristal will remain present in reproductive tissues which are now capable of conception, as proven by the two post-treatment pregnancies in Fine et al.,²⁶ and the three post-treatment pregnancies in Glasier et al.²⁷

Thus approval of Ulipristal as an emergency contraceptive agent puts the FDA in the untenable position of approving a drug which is contraindicated for use in pregnancy, for an indication in which use in pregnancy is inevitable. For this reason alone, the FDA should not approve Ulipristal for use as an emergency contraceptive.

B. Prior to the Consideration of Ulipristal as an Emergency Contraceptive, Thorough Reproduction Toxicity Studies Must Be Completed, and a Mandatory Pregnancy Registry Must Be Established

What happens to the embryo which has been exposed to Ulipristal? The EMEA, after it approved the drug, admitted that it has not required adequate studies to be performed: “Extremely limited data are available on the health of the foetus/new-born in case a pregnancy is exposed to ulipristal acetate. Although no teratogenic potential was observed, animal data are insufficient with regard to reproduction toxicity....”²⁸

Why hasn’t reproductive toxicity been determined for a drug specifically designed to be used in women of childbearing potential when International Conference on Harmonisation guidelines specifically require that such toxicity studies be done?²⁹ The flouting of ICH GCP guidelines

regarding the testing of drugs that may be used by pregnant women for their potential teratogenic effects, places the approval process for ulipristal and NDA 22-474 in a bad light.

The EMEA review noted that the few studies actually performed were grossly inadequate for evaluation of safety:

Doses in these studies were low so as to provide data at levels which did not impair pregnancy. There were no toxicokinetic measures incorporated into these reproductive and developmental toxicity studies. The studies were according to the Applicant not intended to provide safety margins in terms of exposure, but to give data to guide on the consequences of ulipristal acetate administration at dose levels which allowed pregnancies to continue.³⁰

An EMEA document summarizing ulipristal's product characteristics notes the insufficiency of data:

Reproduction toxicity data are insufficient due to lack of human and animal pharmacokinetic data. Due to its mechanism of action, ulipristal acetate has an embryo-lethal effect in rats, rabbits (at repeated doses above 1 mg/kg) and in monkeys. The safety for a human embryo is unknown.³¹

Due to the predictable exposure of two pregnancies to ulipristal per 100 users of the drug, it is critical that full reproductive toxicity studies be done prior to any approval of ulipristal as an emergency contraceptive. Furthermore, complete analysis of the pregnancy registry results referenced by the EMEA should be made available to the FDA and the FDA Reproductive Health Advisory Committee prior to consideration of the Ulipristal NDA.

In addition, a mandatory pregnancy registry system must be established to accurately obtain information on those women who have been exposed to ulipristal. The need for a mandatory registry in the case of Ulipristal is further illustrated by the lack of follow-up information for patients under the best circumstances in the three clinical trials. Incomplete data and/or dropouts (lost to follow-up) includes 106/1241 (8.5%) in Fine et al.,³² 94/1578 (6%) in Creinin et al.,³³ and 134/1899 (7%) in Glasier et al.³⁴ Previous experiences with failed voluntary registries,³⁵ illustrate the need for a mandatory registry to gather accurate information on the teratogenic potential of ulipristal in actual clinical use. Such a registry must be in place prior to approval of Ulipristal as EC.

C. Ulipristal's Label Must Have a Black Box Warning to Warn of Ulipristal's Potential to Cause Abortion and for Meaningful Informed Consent

FDA regulation, 21 C.F.R. § 201.57(c)(1), describes the conditions under which a "boxed warning" are appropriate:

"Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box."

As noted in all three clinical trials (Creinin et al., Glasier et al., and Fine et al.), women who were pregnant took ulipristal. There is no way this can be avoided if ulipristal is approved as an emergency contraceptive; it will be par for the course. Such exposure could lead to the death of the embryo and the abortion of the woman's pregnancy. Since ulipristal is not being approved as an abortifacient it will be necessary for FDA to include a boxed warning notifying health care providers of the drug's abortion-producing properties.

Also, since the teratogenic potential of ulipristal has not been studied, the warning must also include information alerting the patient to the lack of information of the effects of ulipristal on the developing fetus if a pregnancy were to continue after ulipristal treatment AAPLOG believes an appropriate model for the ulipristal black box warning would be the one now present in the misoprostol label. That label contains the following warnings to females who might take that drug:

- ◆ CYTOTEC (MISOPROSTOL) ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION....
- ◆ PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.
- ◆ SPECIAL NOTE FOR WOMEN: Cytotec may cause abortion (sometimes incomplete), premature labor, or birth defects if given to pregnant women.

In this instance misoprostol has been approved for an indication not related to abortion – the prevention of ulcers for those using NSAIDS. Nevertheless, FDA has seen fit to include a boxed warning to indicate that the administration of the drug requires heightened warnings that the drug is an abortifacient. This latter point is of the greatest importance.

Proper informed consent for the use of ulipristal is not possible unless its potential abortifacient actions are made known to women who might take the drug. Many women are not averse to the use of contraceptives that they believe will not disrupt a pregnancy ending their baby's life. They would be morally unwilling to use an abortifacient. Consequently, ulipristal's abortifacient characteristics must be made known to patients through the labeling and by healthcare personnel.

D. Regulatory Parity Between RU-486 and Ulipristal Should Be Enforced

Since ulipristal is a member of a class of drugs, SPRMs, that FDA has found to be dangerous enough to approve pursuant to its restricted distribution regulations, Subpart H, AAPLOG believes that ulipristal should be regulated in an analogous fashion. That is, it should be restricted to use under close supervision of a physician with tracking for specific packages and doses of the medicine. Given the regulatory framework for an SPRM like RU-486, AAPLOG does not see how ulipristal can be approved in a way that lends itself to easy access for use which is necessary for an emergency contraceptive.

III. Off-Label Use and Repeat Use of Ulipristal Will Be a Serious Problem

Experience with the current FDA approved emergency contraceptive levonorgestrel revealed considerable confusion about the frequency and indications for its use, despite written instructions. Thus, multiple use and intentional misuse are serious concerns which are at least acknowledged by EMEA.³⁶

A. Multiple Use per Menstrual Cycle Carries Unknown Safety Risks

The EMEA evaluated the safety of Ulipristal based on the assumption of a single dose correct use per menstrual cycle. On that basis of the assumption of single dose correct use, the EMEA lowered or waived the usually required safety, toxicology and pharmacodynamic study requirements for:

1. Human in vivo metabolism data;³⁷
2. Single dose toxicology studies;³⁸
3. Dose recovery studies;³⁹
4. Carcinogenicity studies;⁴⁰
5. Toxicokinetic documentation;⁴¹
6. Bioavailability and absorption studies;⁴²
7. Mechanism of action with regard to threshold concentration effects;⁴³
8. Formal dose proportionality studies;⁴⁴
9. Information on drug interactions in patients with renal or hepatic impairment;⁴⁵
10. Pharmacokinetic interaction studies.⁴⁶

All of the conclusions about safety were based on this single dose correct use assumption. As the EMEA notes:

Safety data is considered adequate for exposure to 30 mg micronized ulipristal acetate single-dose administration. No long-term safety data is required for the 30 mg formulation, as the indication emergency contraception concerns only a single dose. The subjects were in general healthy women with a mean age of 24 years.⁴⁷

However, actual use will include patients who use the drug more than once during a single menstrual cycle and for whom safety data is not established.⁴⁸

EMEA voiced concern over possible accumulation of ulipristal in the setting of multiple doses:

Following intravenous and oral administration of ¹⁴C-ulipristal acetate to rats and monkeys, radioactivity was widely distributed. In rats, concentrations of radioactivity declined after peak levels, but quantifiable radioactivity levels were still present in all tissues at the final sampling time of 3 days. In addition, in monkeys even after 14 days radioactivity was measurable in all investigated tissues. The liver accounted for the majority of radioactivity in the tissues in the distribution studies in rat and monkey. However, ulipristal acetate also showed a high tissue to plasma ratio in the kidney, clitoris, ovary, uterus, adrenal, fat, uveal

tract, pigmented skin and mucosa of the gastro-intestinal tract, indicating accumulation in these organs if the drug is used again a month later. *Most likely this has no implications, because ulipristal acetate is given as a single dose, but in repeated dose this could result in toxicity due to accumulation.*⁴⁹

Actual use in the clinical setting will not only involve safety considerations for women who use the drug multiple times but also involve women in especially vulnerable populations in which ulipristal safety has not been established. Other unstudied populations of concern include:

1. Women over age 35;
2. Women who are on concomitant hormonal contraceptives (use for “missed pill” contraceptive failure);⁵⁰
3. Lactating women;⁵¹ and
4. Adolescent females, for whom no safety or efficacy studies have been done.

The adverse events reported during the clinical trials include a profile of increased infections and bleeding disturbances not surprisingly similar to the adverse events reported for mifepristone.⁵² The increase in infections is predictable based on the significant, albeit somewhat less profound, ulipristal blockade of glucocorticoid receptors on immune cells in the human.⁵³

Yet even more disturbing are the reports of ovarian pain (common) and ovarian cyst formation in clinical trial participants. In three patients the cyst formation did not resolve; which resulted in two cases of surgery: one exploratory surgery for ruptured cysts and one surgical removal of an ovary.⁵⁴

Thus, although the EMEA approved safety in single dose single use per cycle investigations, the safety of predictable multiple uses per cycle has not been established, nor have the relevant basic pharmacokinetic or pharmacotoxicological studies been carried out to allow a reasonable prediction of what risks under these circumstances might be. Thus the current NDA for Ulipristal approval in the U.S. must be considered deficient until such basic safety studies under situations of multiple use are submitted.

B. Ulipristal’s Known Abortifacient Mechanism, Similar to That of RU486, Makes It Highly Likely It Will Be Used Off-Label as an Abortifacient

The EMEA identified potential off label use as an abortifacient as a safety concern for the approval of Ella One.⁵⁵ The European Medicines Agency’s has taken matters to the point of discussing monitoring options with the drug sponsor, Laboratoire HRA Pharma; yet the remedies they suggested are impotent to prevent such abuse:

The applicant has discussed the following options to monitor intended off-label use of Ellaone:

1. Self-reporting of prescribers,

2. Retrospective survey in Ob/gyn departments among women who are hospitalized for incomplete “spontaneous” abortions or miscarriage,
3. Use of prescription registries to identify off-label prescriptions.

It is acknowledged that all these approaches suffer from similar, inevitable limitations (prescribers may not report information about off-label prescriptions).⁵⁶

In fact the safety issues surrounding this off label use involve not only teratogenic potential as previously discussed, but potentially more significant, dose-response adverse events. Since the potential for off label use of this drug is so great, the FDA should require that at the very least, complete reproductive toxicology studies and safety studies be completed and submitted to the FDA for evaluation prior to consideration of Ulipristal approval for emergency contraception.

IV. The Surreptitious Use of Ulipristal Must Be Prevented

Ulipristal poses a unique danger for the general public in that it is a drug perfectly suited for the surreptitious use on an unsuspecting, pregnant woman. The same would be true for RU-486, but FDA’s restrictions on its physical distribution make its criminal misuse unlikely. AAPLOG believes that FDA must institute some form of highly controlled distribution of ulipristal that would make its criminal use impossible.

An internet search will easily produce stories about men who have been arrested or convicted of surreptitiously using an abortifacient on an unsuspecting woman. Typically, because the drug is more widely available, the drug used is misoprostol. A Swedish case fits that profile, and a Briton obtained both misoprostol and mifepristone illegally.⁵⁷ Not to be outdone, news accounts from Pennsylvania and Maryland have described actions by men who used the synthetic animal hormone, Prostaglandin, a drug used to induce the bovine abortion of a calf.⁵⁸ (The use of Prostaglandin does not appear to have been successful.)

In the United States, the most notorious case involved the surreptitious use of RU-486 on a Wisconsin woman causing the abortion of her pregnancy. In November 2007, an Appleton, Wisconsin resident Manishkumar M. Patel was charged with attempted first-degree intentional homicide of an unborn child. The charges made national news because Patel allegedly gave RU-486 to his pregnant girlfriend, causing a miscarriage. She did not know she was being given the drug.

An Indian immigrant, Patel was involved in an extramarital affair with the victim and fathered a son by her in 2004. Prosecutors say he did not want another child and upon hearing the news in August 2007 that she was again pregnant Patel acted. He became uncharacteristically attentive and even prepared meals for his girlfriend. She became suspicious of his behavior after noticing powder on the rim of a cup containing a smoothie he had prepared for her at an ice cream store.

Patel's girlfriend did not drink the smoothie, feigning ill health but saved a sample of the powder. Later, she experienced difficulties with her pregnancy and contacted a lab to obtain a test kit. Before it arrived, she miscarried. The lab subsequently identified the powder as RU-486. Even more distressing was the fact that she had also miscarried in September 2006.

A search of Patel's residence uncovered a cache of RU-486 pills, which he admitted had come from India. India classifies RU-486 as a prescription drug, but there is lax supervision of its distribution. Consequently, RU-486 can be purchased on something approaching an over-the-counter basis. Thus, it is not surprising that Patel admitted bringing the drugs from India where they are available and inexpensive. Patel and his wife fled, and authorities in Wisconsin still want to prosecute him.

FDA should learn an important lesson from the cases of the Briton, the Swede, and Mr. Patel. That is, no SPRM – like RU-486 or ulipristal – can be released into the loosely regulated commercial stream of pharmaceutical products. Unlike misoprostol which quickly brings on uterine contractions when taken by a pregnant woman, RU-486 and ulipristal would operate as silent killers only producing symptoms of a typical miscarriage. For example, it is quite likely that Patel's girlfriend was poisoned in 2006 prompting an earlier miscarriage of which she was completely unaware. Had he not been careless later, Patel would have completed a second abortion without detection. One can only wonder how often this happens in India. This pattern of behavior should not be allowed to develop in the United States.

Restricted Distribution Is Needed to Prevent Surreptitious Use and Off-label Abuse of the Drug as an Abortifacient

We believe FDA has at least two models to which it can look for guidance -- the iPLEDGE and S.T.E.P.S. distribution systems. Since 1972, restrictive access programs have been utilized for several medications as part of a combined effort between manufacturers and the FDA. These programs were developed as a result of concerns over serious adverse effects, abuse potential, teratogenicity, and/or effort to ensure prescribing in a manner that limits patient risk. iPLEDGE is a computer-based risk management program that aims to eliminate fetal exposure to isotretinoin (Accutane[®]) through an FDA-approved restricted distribution program. S.T.E.P.S. is an FDA-approved program designed to reduce exposure to thalidomide (Thalomid[®]).

A three step system should be established for ulipristal. First, a physician would assign a patient ID to maintain privacy then the physician or person under their supervision would register the patient online after completing counseling and pregnancy screening. Second, the patient would be required to complete a survey either via telephone or online utilizing the ID assigned by the physician. Third, prior to dispensing a prescription for ulipristal, a pharmacist would verify online that the physician and patient had completed the necessary steps. A system like this could serve to prevent a black market from developing for ulipristal.

Clearly, a restricted distribution system must be put in place if ulipristal is approved in order to protect the health and safety not only of prescribed users but also of the public at large.

V. Conclusion

In conclusion, AAPLOG does not believe ulipristal should be approved for use in the United States because it will act as an abortifacient in many of the women for whom it will be prescribed.

Since FDA appears to be determined to approve this abortifacient as a contraceptive, FDA must place restrictions on its distribution and marketing as outlined above in Sections II, III, and IV. For example, it must require that women are informed of its abortifacient properties and that case histories of babies exposed to it are placed in an appropriate tracking system that follows them until they reach majority.

Sincerely,

/s/ Donna J. Harrison, M.D.

President

American Association of Pro Life Obstetricians & Gynecologists

NOTES

¹ 75 Fed. Reg. 22146 (Apr. 27, 2010).

² Ulipristal acetate is also known by as: ulipristal, CDB-2914, VA2914, HRP-2000, RTI-3021-012, and EllaOne[®].

³ Dear Colleague Letter of FDA Commissioner Margaret A. Hamburg (April 21, 2010) (regarding advisory committees, transparency, and financial disclosure).

⁴ Id.

⁵ See, for example, the reviews presented on FDA's mifepristone webpage (LINK: < http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_mifepristone.cfm >).

⁶ European Medicines Agency, "CHMP Assessment Report for EllaOne," (Doc.Ref.: EMEA/261787/2009), p. 8. Hereinafter, "EMEA CHMP Assessment." See also Attardi et al., "In vitro Antiprogesterone/Antiglucocorticoid Activity and Progesterone and Glucocorticoid Receptor Binding of the Putative Metabolites and Synthetic Derivatives of CDB-2914, CDB-4124, and Mifepristone," 88 *Journal of Steroid Biochemistry & Molecular Biology* (2004): 277-288, 286.

⁷ EMEA CHMP Assessment, p. 17. This means: 1) that the endometrial glands which grow, or "proliferate" in order to be able to provide an implantation site for the embryo cannot grow, and thus the embryo's implantation is obstructed; 2) that if the embryo has already implanted, then the "inhibition of progesterone induced endometrial glandular proliferation" indicates that the endometrial glands cannot grow to become the placenta. In fact, the maternal side of the placenta, which is fed by progesterone, would atrophy upon ingestion of ulipristal. This is the same mechanism of action one finds in the abortifacient mifepristone or RU-486.

⁸ EMEA, Product Information Annex I (19/03/2010 Ellaone-H-C-1027-IA-04) (updated May 7, 2010): sec. 5.3 ("Preclinical Safety Data"), p. 7.

⁹ Reel et al., "Antioviulatory and Postcoital Antifertility Activity of the Antiprogesterone CDB-2914 When Administered as Single, Multiple, or Continuous Doses to Rats," 58 *Contraception* (1998): 129-136, p. 129 (abstract). See also EMEA CHMP Assessment, p. 11. The EMEA noted, "Treatment of cell cultures with 100 µM ulipristal acetate significantly inhibited estrogen and progesterone stimulated proliferation of endometrial stromal cells."

¹⁰ VandeVoort et al., "Effects of Progesterone Receptor Blockers on Human Granulosa-Luteal Cell Culture Secretion of Progesterone, Estradiol, and Relaxin," 62 *Biology of Reproduction* (2000): 200-205, 200. In this article, ulipristal is referred to as "HRP-2000."

¹¹ Hild et al., "CDB-2914: Anti-progestational/antiglucocorticoid Profile and Post-coital Anti-fertility Activity in Rats and Rabbits." 15 *Human Reproduction* (2000): 822-829, 824.

¹² Chun-Xia Meng, "Levonorgestrel Emergency Contraception: Effects on Endometrial Development and Embryo Implantation" (Stockholm, Sweden: Karolinska Institutet, 2009): p. 19.

¹³ As Gacek has demonstrated, no consensus exists in the four major American medical dictionaries for the proposition that either "pregnancy" or "conception" begin or occur with implantation. Christopher M. Gacek, "Conceiving 'Pregnancy': U.S. Medical Dictionaries and Their Definitions of 'Conception' and 'Pregnancy,'" *National Catholic Bioethics Quarterly* (Autumn 2009): 554-557. That said, embryocidal mechanisms of action 2 and 3 destroy an implanted embryo which satisfies the definition of "pregnancy" from all authorities.

¹⁴ EMEA, Product Information Annex I (19/03/2010 Ellaone-H-C-1027-IA-04) (updated May 7, 2010): sec. 4.6 ("Pregnancy and Lactation"), p. 4.

¹⁵ Fine et al., "Ulipristal Acetate Taken 48-120 Hours After Intercourse for Emergency Contraception," 115 *Obstetrics & Gynecology* (Feb. 2010): 257-263, 260.

¹⁶ Creinin et al., "Progesterone Receptor Modulator for Emergency Contraception A Randomized Controlled Trial," 108 *Obstetrics & Gynecology* (Nov. 2006): 1089-1097, 1092.

¹⁷ Glasier et al., "Ulipristal Acetate Versus Levonorgestrel for Emergency Contraception: A Randomised Non-inferiority Trial and Meta-analysis," *The Lancet* (published online)(Jan. 29, 2010): 1-8, 4.

- ¹⁸ Fine et al., p 260.
- ¹⁹ Creinin et al., p 1092.
- ²⁰ Glasier et al., p. 4.
- ²¹ Fine et al., p. 259.
- ²² Creinin et al., p. 1092.
- ²³ Glasier et al., p. 4.
- ²⁴ EMEA, Product Information Annex I (19/03/2010 Ellaone-H-C-1027-IA-04) (updated May 7, 2010): sec. 5.2 (“Pharmacokinetic properties,” subsection: “Metabolism/elimination”), p. 7.
- ²⁵ EMEA CHMP Assessment, p. 13
- ²⁶ Fine et al., p 260.
- ²⁷ Glasier et al., p. 4.
- ²⁸ EMEA, Product Information Annex I (19/03/2010 Ellaone-H-C-1027-IA-04) (updated May 7, 2010): sec. 4.6 (“Pregnancy and Lactation”), p. 4.
- ²⁹ ICH M3 (R2): Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (current Step 4 ver., date June 11, 2009): sec. 11.3 (“Women of Childbearing Potential”), p. 18. ICH M3 (R2) provides this guidance regarding trials involving women who can bear children:

For women of childbearing potential (WOCBP) there is a high level of concern for the unintentional exposure of an embryo or fetus before information is available concerning the potential benefits versus potential risks. The recommendations on timing of reproduction toxicity studies to support the inclusion of WOCBP in clinical trials are similar in all ICH regions.

It is important to characterize and minimize the risk of unintentional exposure of the embryo or fetus when including WOCBP in clinical trials. One approach to achieve this objective is to conduct reproduction toxicity studies to characterize the inherent risk of a drug and take appropriate precautions during exposure of WOCBP in clinical trials. A second approach is to limit the risk by taking precautions to prevent pregnancy during clinical trials. Precautions to prevent pregnancy include pregnancy testing (*e.g.*, based on the β -subunit of HCG), use of highly effective methods of birth control (Note 3), and study entry only after a confirmed menstrual period. Testing for pregnancy during the trial and subject education should be sufficient to ensure compliance with the measures designed to prevent pregnancy during the period of drug exposure (which could exceed the length of study). To support these approaches, informed consent should be based on any known pertinent information related to reproduction toxicity, such as a general assessment of potential toxicity of pharmaceuticals with related structures or pharmacological effects. If no relevant reproductive information is available, the potential for unidentified risks to the embryo or fetus should be communicated.

For more on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), go to: < www.ich.org >.

- ³⁰ EMEA CHMP Assessment, p. 15 (in the subsection “Reproductive Toxicity”).
- ³¹ EMEA, Product Information Annex I (19/03/2010 Ellaone-H-C-1027-IA-04) (updated May 7, 2010): sec. 5.3 (“Preclinical Safety Data), p. 7.
- ³² Fine et al., p. 259.
- ³³ Creinin et al., p. 1092.
- ³⁴ Glasier et al., p. 4.

³⁵ Julie Robertson et al., "A Survey of Pregnant Women Using Isotretinoin," *73 Birth Defects Research (Part A): Clinical and Molecular Teratology* (Nov. 2005): 881-887, Abstract. Text from the article's abstract:

RESULTS: Almost 1/4 of the women surveyed (24%; 8/34) did not recall having contraception counseling before starting their medications. Once therapy was initiated, 62% (21/34) recalled using a birth control method, but only 29% (6/21) recalled using 2 forms of birth control, as specified by the voluntary pregnancy prevention programs. Monthly pregnancy tests were not always conducted during treatment, as recalled by the surveyed women (56%; 19/34). As many as 24% (8/34) of the women surveyed recalled that they were not screened using 2 pregnancy tests before receiving a prescription, another recommendation of the programs. Only a small number of the women (30%; 6/20) in the United States recalled being enrolled in any manufacturers' voluntary pregnancy prevention survey.

³⁶ EMEA CHMP Assessment, p. 13 ("...because ulipristal acetate is given as a single dose, but in repeated dose this could result in toxicity due to accumulation.").

³⁷ EMEA CHMP Assessment, pp. 14, 18.

³⁸ EMEA CHMP Assessment, p. 14.

³⁹ EMEA CHMP Assessment, p. 14.

⁴⁰ EMEA CHMP Assessment, p. 15.

⁴¹ EMEA CHMP Assessment, p. 16.

⁴² EMEA CHMP Assessment, p. 20.

⁴³ EMEA CHMP Assessment, p. 20.

⁴⁴ EMEA CHMP Assessment, pp. 21-22.

⁴⁵ EMEA CHMP Assessment, p. 21. Here is an example of one EMEA waiver based on the idea that only one dose would be taken per menstrual cycle:

Ulipristal acetate is metabolised by cytochrome P450 co-enzymes in the liver. Therefore, liver impairment can influence the pharmacokinetics of ulipristal acetate in a significant way. However, as Ellaone is administered only once and most likely to healthy young females liver impairment will probably not influence the efficacy and safety of ulipristal acetate in a clinically significant way.

⁴⁶ EMEA CHMP Assessment, p. 22.

⁴⁷ EMEA CHMP Assessment, p. 35.

⁴⁸ EMEA CHMP Assessment, p. 35. Repeat users were known to have been enrolled in the clinical trials:

Seventy-five women were enrolled on multiple occasions in the phase III study (66 twice and 9 three times). Multiple enrollers were defined as subjects who were enrolled and treated more than once.

⁴⁹ EMEA CHMP Assessment, p. 13 (emphasis added).

⁵⁰ EMEA CHMP Assessment, p. 44. The EMEA states:

Because ulipristal acetate binds the progesterone receptor with high affinity, it may interfere with the action of progestogen-containing medicinal products:

- Contraceptive action of combined hormonal contraceptives and progestogen-only contraception may be reduced.
- Concomitant use of ulipristal acetate and emergency contraception containing levonorgestrel is not recommended. Hormonal contraceptives are known to decrease the efficacy of Ulipristal.

⁵¹ EMEA CHMP at page 21 (“It is unknown whether ulipristal acetate is excreted in human or animal breast milk. Ulipristal acetate is a lipophilic compound and may theoretically be excreted in breast milk. A risk to the breast-fed child cannot be excluded.”).

⁵² EMEA CHMP at page 38 (table of adverse reactions). *See also* Margaret M. Gary and Donna J. Harrison, “Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient,” 40 *Annals of Pharmacotherapy* (2006): 191-7 (published online Dec. 27, 2005) (www.theannals.com).

⁵³ Ralph P. Miech, “Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium Sordellii*,” 39 *Annals of Pharmacotherapy* (2005): 1483-1488.

⁵⁴ EMEA CHMP Assessment, p. 36.

⁵⁵ EMEA CHMP Assessment, p. 41.

⁵⁶ EMEA CHMP Assessment, pp. 45-46.

⁵⁷ For example, there have been numerous reports of surreptitious administration of drugs to pregnant women in the last ten years. Perhaps, the most notorious was that of U.K. resident, Gil Magira, who illegally obtained both RU-486 and misoprostol and gave them to his wife. Frances Gibbs, “‘Loner’ Husband Tried to Abort Child by Hiding Pills in Wife’s Breakfast,” *The Times* (London) (March 1, 2008). In what appears to have been a misoprostol-only induced abortion, a Swedish man was convicted of aggravated assault and given a whopping 18-month sentence. Associated Press, “Court: Swedish Man Put Abortion Pills in Lover’s Food,” Feb. 26, 2008.

⁵⁸ Fortunately, both abortion attempts using the synthetic animal hormone were unsuccessful.