

Ella[®]: Muddying the Waters

by Julie Lynch McDonald, Pharm.D.

Ella[®] (ulipristal) was approved by the FDA in August of 2010 for emergency contraception (EC) within 120 hours of intercourse. Despite recent approval, many concerns and questions regarding ulipristal remain unanswered. This article will examine ulipristal, highlight key concerns, and detail practical ways Christian pharmacists can make a difference. However, to begin one must first understand Plan B[®] (levonorgestrel) and Mifeprex[®] (mifepristone), which came before and led to the development of ulipristal.

Plan B[®]: An Overview

Plan B[®] (levonorgestrel), or the “morning after pill,” was the first medication approved by the FDA for EC in 1999 and later in 2006 achieved OTC status with age restrictions. Levonorgestrel is a progestin used for more than 30 years for hormonal contraception typically at 0.1-0.15mg per day. Levonorgestrel was traditionally used off-label for EC through various high dose regimens (generally 1.5mg), which led to Plan B[®]. The primary intent of EC administration of levonorgestrel is to inhibit or delay ovulation, but it can also potentially prevent fertilization by affecting tubal transport of egg and/or sperm. In addition, levonorgestrel can theoretically decrease the receptiveness of the endometrium for implantation.¹ Potential for post-fertilization effects has led to much debate, even among Christians, on whether levonorgestrel and various forms of hormonal

contraception should be considered abortifacients.

Approval of Plan B[®] was alleged to be the solution to the rising number of unplanned pregnancies and the key to decrease abortion rates, but this has not occurred as EC efficacy of Plan B[®] was “overestimated”.² In fact, 10 separate studies showed providing a supply of EC to be kept at home produced a nearly threefold increase in use, but effects on pregnancy and abortion rates were unmeasurable.³ There are no known effects of Plan B[®] post-implantation.¹

Mifeprex[®]: An Overview

Mifeprex[®] (mifepristone), or the “abortion pill,” was approved by the FDA in September of 2000 for medical abortions of pregnancies ≤49 days since the start of the last normal period (LMP) or a clinically useful window of 3 weeks. The history behind mifepristone’s approval is riddled with unprecedented politics and controversy, which would require a separate article to detail.

Mifepristone is a first generation progesterone receptor modulator (PRM). Progesterone is required to begin and maintain pregnancy, therefore PRMs were synthetically designed to bind and inactivate the progesterone receptor with a significantly higher affinity than progesterone. As a result, the progesterone-dependent endometrium priming, placental development, and suppression of endometrial contractility does not occur, thus PRMs cause an implanted

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About the Author

Julie Lynch McDonald received her Doctor of Pharmacy degree in May 2008. Following graduation, Julie spent two years working at an independent retail pharmacy in south Florida, and recently relocated to accept a pharmacist-in-charge position at Whale Tail Pharmacy in Craig, Alaska, where she is developing an experiential rotation site for students. She has been a member of CPFI’s Board of Directors since June of 2007, and specifically serves to oversee student chapters and recent graduates. Additionally, Julie conducts in-depth research on abortifacients and provides education presentations on this topic in a variety of settings.

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fetus to detach from the uterine lining ending fetal food and oxygen supply. However, early clinical testing revealed mifepristone alone failed to consistently result in complete vaginal expulsion.⁴ Therefore, the FDA approved regimen requires misoprostol to be administered 2 days after mifepristone to cause softening of the cervix and uterine contractions hence chemically assisting/forcing vaginal expulsion of placenta and fetus. It is important to note a medical abortion with mifepristone requires use of misoprostol (a combination this article will subsequently refer to as RU-486).

RU-486 was perceived as a means to mainstream abortion, but has remained relatively unpopular in comparison to expectations due to multiple factors (used for approximately 25% of U.S. abortions or 184,000 users in 2008). First, RU-486 is not an alternative for surgical abortions as 1 in 12 users, a conservative estimate based on the sole U.S. uncontrolled trial, will require surgery after RU-486 due to continued pregnancy, retained tissue, and/or uncontrolled hemorrhage.⁶ Secondly, RU-486 is less effective than surgical abortions and contains higher risk for specific complications, such as bleeding and infection.⁷ For example, the risk of maternal death due to infection alone is ≥ 10 times higher with mifepristone vs. surgical abortion.⁸ In the U.S., there have been 7 known maternal deaths specifically related to RU-486. Sadly the true number of deaths remains unknown, as most deaths were reported by California where extraordinary regional awareness “stimulated reports of additional cases that may have not been detected in other states.”⁹ There is no systematic tracking for RU-486 outcomes or adverse events. Furthermore, failure to follow up after RU-486 has been a considerable problem. A Seattle abortion provider, Suzanne Poppema, stated they are “lucky if 30-40% of patients” return for follow up.¹⁰

The only remaining claim in favor of RU-486 is use of medications is less physiologically traumatizing than surgery. However, surgical abortion involves a woman in a room with healthcare professionals, she does not personally witness the procedure, and it is over that same day. During RU-486, a woman is often alone for an extended period of abdominal cramping, bloody vaginal discharge, nausea, diarrhea, and/or headache followed by vaginal expulsion of fetus and placenta, which the woman will be responsible for disposal. This is compounded by the habitual lack of preparation women receive as they are told to simply anticipate a heavy period. The former chairman of the company that patented RU-486 stated “A woman has to ‘live’ with her abortion for at least a week using this technique. It’s an appalling psychological ordeal.” The company spokesman offered more insight by

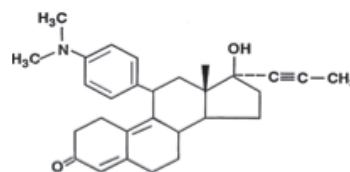
noting “When [women] take a pill, they have the feeling they are truly responsible for the abortion.”¹¹ During a RU-486 trial in France, a nurse recalled observing 6 embryos in 6 surgical dishes by a sink. She called the experience “upsetting... like looking at a little row of people” and stated “women too were shocked when they looked at what they had expelled.”¹² The emotional strain was observed during the U.S. RU-486 trial when a woman was hospitalized for depression after attempting suicide.¹³

Why ulipristal?

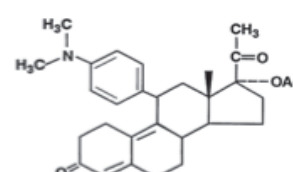
A basic understanding of Plan B[®] and RU-486 reveals their differences and fundamental flaws. Plan B[®] has limited efficacy to prevent pregnancy. Meanwhile, RU-486 is effective at aborting pregnancies yet contains risk for complications and adverse events leading to a stigma of questionable safety. Ulipristal is viewed as the solution. It will be marketed as EC similar to Plan B[®], despite the fact that it is actually a modified version of an undisputed abortifacient, mifepristone.

What is ulipristal?

Ulipristal and mifepristone are chemically identically aside for a substitution on the 17th carbon, which results in ulipristal containing a higher oral anti-progestational potency and lower anti-glucocorticoid effects.^{14,15} Ulipristal is classified as a second generation PRM and its action on ovarian and endometrial tissue is indistinguishable from mifepristone.^{16,17} At low doses, ulipristal and mifepristone can suppress/prevent ovulation, thus acting as EC. However, ulipristal and mifepristone are also powerful pure progesterone antagonists thus unavoidably resulting in post-fertilization and post-implantation effects.¹⁵ The European Medicines Agency’s Assessment Report found in repeated dose animal studies, “as expected, ulipristal acetate is embryotoxic at low doses,” and an intentional effort was made to remove mention of ulipristal’s abortifacient potential from the report in hopes of deterring off-label use for medical abortions.^{16,a}



Mifepristone



Ulipristal

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Will ulipristal cause a medical abortion?

Based on the data available overall conclusions on the “embryo-lethal potential” of ulipristal remain “uncertain.”¹⁶ To put it candidly, studies have not been completed to prove or disprove ulipristal’s ability to abort an implanted embryo in humans. However, ulipristal was found after oral administration to be more potent than mifepristone as an abortifacient in rats and just as potent in monkeys.^{17,18} Therefore, animal testing for ulipristal, human data for mifepristone, and common sense indicates ulipristal can and will cause a medical abortion.

What effect will ulipristal have on pregnancies?

To be realistic, use of ulipristal by pregnant women will be unavoidable. Proper use of pregnancy tests will not completely prevent this, as these tests require ≥ 12 days after conception to accurately detect pregnancy. Even within carefully controlled parameters of 3 phase III trials, ulipristal was administered to women who were later judged to be already pregnant.^{2,20,21} Granted the percentage of already pregnant women was relatively small, but when the FDA approved ulipristal they failed to require pregnancy testing prior to administration as was conducted in trials. For this reason among others, the number of pregnant women prescribed ulipristal is bound to increase when used outside the trial setting. Use of ulipristal by pregnant women exposes an embryo to an embryotoxic agent for >6.5 days based on available terminal half-life data.¹⁶

Whether used by an already pregnant woman or if pregnancy continues after ulipristal use, there is concern for resulting ectopic pregnancies, incomplete abortions, and birth defects.¹⁶ Two trials reported pregnancy outcomes for women who used ulipristal, and the result was 90% ended in miscarriage for those with known outcomes that did not choose to abort.^{21,b} Prior to approval of Plan B[®], the FDA required testing of maternal and fetal safety, yet this has not been determined for ulipristal.

Will ulipristal result in infections and complications similar to RU-486?

The HHS Emerging Clostridial Disease Workshop found RU-486 was associated with infections, which resulted in “rapid fulminating lethal shock syndrome.” The workshop further established the clostridial infections associated with RU-486 were unlikely to be prevented through prophylactic antibiotics, an effective treatment has not been identified, and these infections have been 100%

fatal. The cause of RU-486 associated infections is two-fold: mifepristone suppresses the immune system through its innate anti-glucocorticoid effects and at the same time the aborting uterus serves as a medium for bacterial growth.⁹ Consequently, it is very distressing that the ability of ulipristal to cause similar infections as well as severe hemorrhage was not well-studied prior to approval.

Will ulipristal help prevent unplanned pregnancies?

Two trials found ulipristal was not inferior to Plan B[®], but a superiority trial has not been completed.²² Furthermore, two trials examined use of ulipristal after >72 hours since intercourse. One trial stated “further investigation” was needed for those >72 hours due to their limited population, and the other trial failed to reach power for safety or efficacy of those >72 hours.²¹ Yet, the FDA approved ulipristal use up to 120 hours since intercourse.

Summary on ulipristal

A lesson should have been learned from the calamity surrounding approval of RU-486, yet in a similar fashion ulipristal was approved without thorough evaluation despite evidence of safety concerns. The FDA recommended numerous follow-up studies to answer concerns that still lingered at the time of RU-486’s approval. In 10 years these studies have not been completed due to enrollment issues.²² The FDA’s unwillingness to learn from the past has yet again left the medical community with many unanswered concerns, such as ulipristal’s effect if used by pregnant women or if pregnancy occurs after use, risk of infection and hemorrhage, efficacy if used after >72 hours, and safety in the general population or if used repeatedly.

Since most healthcare professionals are currently unaware of the differences between Plan B[®] and RU-486, introduction of ulipristal appears to be an attempt to capitalize on this confusion by modifying a known abortifacient, but marketing it as EC. It does not end there. Evidence indicates in the near future there may be efforts to submit a supplemental application for ulipristal to be used once monthly for birth control and/or achieve OTC status. Presently efforts to develop continual use (i.e. once monthly dosing) have been delayed due to endometrial safety concerns, but this then points back to the unaddressed concern of ulipristal’s safety if used repeatedly for EC.

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Unlike RU-486, which is provided directly by clinics or physicians, pharmacists will be directly involved with ulipristal as it will be available by prescription.

What can Christian pharmacists do?

Since mifepristone was approved, pro-life advocates have pointed to the >1,000 adverse events reports submitted to the FDA among other facts calling RU-486 unsafe for women. Meanwhile, pro-choice advocates have called these events isolated and defended RU-486 as a good option for women. In the absence of systematic tracking for the true incidence of adverse events, these debates will undoubtedly continue regarding ulipristal. The unfortunate result is physicians and women are left without the necessary information to make sound medical decisions and public health policy is determined by politics rather than facts.

However, opportunity exists for pharmacists to serve a pivotal role in positively influencing public health policy. For instance, pharmacists can advocate for and contribute towards designing an innovative restrictive distribution system for ulipristal with the intent of ensuring proper patient selection and counseling, tracking adverse events, monitoring effects of off-label use, and/or tracing outcomes. This would allow pharmacists to provide leadership in demanding the necessary information required to guide public health policy is assembled and once a system is established pharmacists would be responsible for consistently and reliably accumulating this essential data. Additionally, pharmacists can be vital to ensuring ulipristal does not achieve OTC status or approval for once monthly use due to the obvious health risks these policy changes would have for women.

Most importantly, Christian pharmacists need to actively serve as a source of truthful information for the public and healthcare professionals. This can be accomplished through conducting research for organizations or government agencies, authoring publications for local newspapers or professional journals, confidently and straightforwardly counseling patients, providing in-services for crisis pregnancy centers, delivering presentations at professional meetings, involvement in hearings and discussions on future health policy changes, and seeking additional opportunities as God provides. Through the CPFI National Student Council (NSC), student chapters nationwide will be engaging in just such an outreach through their upcoming "R U Aware" educational campaign under the leadership of NSC chairperson Amanda Davis.

Closing Thoughts

As pharmacists, we are trained to rely on medications for solutions. However, when it comes to unplanned pregnancy, history reveals the more pills we throw at the problem, the more problems we create. As a woman and healthcare professional, I hope we will begin to proactively address unplanned pregnancy rather than continually resort to jeopardizing women's health with afterthought solutions. Nevertheless, these afterthought solutions do exist and there is a cry for Christian pharmacists to be more actively involved. RU-486 should have been a wake-up call, but as a whole we were complacent and debated between ourselves if life began at fertilization or implantation. Meanwhile, hard at work was an agenda that places their perceived collective societal good from ending unplanned pregnancies over the health of individual women, not to mention the life of the unborn. God specially equipped each Christian pharmacist to be a drug expert and an earthly representation of Jesus Christ. Seems rather obvious, Christian pharmacists have a responsibility to be actively involved on this issue.

References

1. Bastianelli C, Farris M, Benagiano G. Emergency contraception: a review. *Eur J Contracept Reprod Health Care*. Mar 2008;13(1):9-16.
2. Glasier AF, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. *The Lancet*. Jan 2010.
3. Reinberg S. Emergency Contraception Doesn't Lower Abortion Rates. *Health Day News*. www.sexualhealth.e-healthsource.com (accessed 2010 Jun 24).
4. Elia D. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York, New York, Plenum Press. 1985;211-20.
5. Johnson LA. Abortion Pill Used in a Quarter of US Abortions. www.physorg.com/news166292010.html (accessed 2010 Sept 2010).
6. Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med*. 1998;338:1241-7.
7. Gary MM, Harrison DJ. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. *Ann Pharmacother*. 2006;40(2):191-7.

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8. Souder ME. The FDA and RU-486: Lowering the Standard for Women's Health. www.usccb.org/prolife/issues/ru486/SouderStaffReportonRU-486.pdf (accessed 27 Feb 2009).
9. Department of Health and Human Services. Emerging Clostridial Disease Workshop Summary of Proceedings. May 2006.
10. Fact Sheet on Mifepristone/Misoprostol Abortion: FDA Rejects Safeguards Used in China, France, Sweden and the United Kingdom. www.nccbuscc.org/prolife/issues/abortion/ru486factsheet.shtml (accessed 23 Sept 2010).
11. RU486Facts Organization. Medical Information About RU-486 (Mifepristone). www.ru486facts.org/index.cfm (accessed 14 Feb 2007).
12. Life Issues Institute. RU486 Not as Easy as Promised, Says Women and Abortionist. www.lifeissues.org/ru486/ru4862000/ru00-11.html (accessed 18 Feb 2007).
13. Rarick L. Reproductive Health Drugs Advisory Committee, Hearing Transcript FDA. 19 July 1996:134.
14. Larner JM, Reel JR, Blye RP. Circulating concentrations of the antiprogestins CDB-2914 and mifepristone in the female rhesus monkey following various routes of administration. *Hum Reprod.* 2000;15(5): 1100-06.
15. Hild SA, Reel JR, Hoffman LH, Blye RP. CDB-2914: Anti-progestational/anti-glucocorticoid profile and post-coital anti-fertility activity in rats and rabbits. *Hum Reprod.* 2000;15(4):822-829.
16. European Medicines Agency. CHMP Assessment Report for Ellaone. Doc.Ref.: EMEA/261787/2009.
17. Teutsch G, Philibert D. History and perspectives of antiprogestins from the chemist's point of view. *Hum Reprod.* 1994;9:12-31.
18. Tarantal AF, et al. Effects of two antiprogestins on early pregnancy in the long-tailed macaque. *Contraception.* 1996;54:107-15.
19. Attardi, et al. In vitro Antiprogestational/Antiglucocorticoid Activity and Progesterone and Glucocorticoid Receptor Binding of the Putative Metabolites and Synthetic Derivatives of CDB-2914, CDB-4124, and Mifepristone. *J Steroid Biochem Mol Biol.* 2004;277-88.
20. Creinin MD, et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. *Obstet Gynecol.* 2006;108(5):1089-97.
21. Fine PT, et al. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception.

Obstet Gynecol. 2010;115(2):1-7.

22. Woodcock J. Statement before Subcommittee on Criminal Justice, Drug Policy and Human Resources of the Committee on Government Reform. 17 May 2006.

Endnotes

- a. Image modified from Larner JM, Reel JR, Blye RP. Circulating concentrations of the antiprogestins CDB-2914 and mifepristone in the female rhesus monkey following various routes of administration. *Hum Reprod.* 2000;15(5): 1100-06.
- b. Fine, et al. had 26 pregnancies in those treated with ulipristal (15 aborted, 5 spontaneous abortions, 5 unknown status, and 1 born healthy), Creinin, et al. had 7 continued pregnancies in those given ulipristal (no further information provided), and Glasier, et al. had 20 continued pregnancies in those given ulipristal (14 aborted, 4 spontaneous abortions, 2 unknown). Therefore, only Fine and Glasier provided information on pregnancies after ulipristal use, and there were 17 where women did not elect to abort the pregnancy. Thus, the combined results from Fine and Glasier found 9 out of 17 (53%) of these pregnancies ended in spontaneous abortion or miscarriage, plus another 7 out of 17 (41%) had an unknown outcome. Therefore, after three phase III trials, complete outcomes have been provided for 10 pregnancies where women did not choose to abort after being administered ulipristal, and 9 out of 10 (90%) ended in spontaneous abortion or miscarriage.