

Brand Name: Ella®

Generic Name: ulipristal acetate

Manufacturer¹: Watson Pharmaceuticals, Inc.

Drug Class^{1,2,3}: Emergency Contraceptive, Progesterone agonist/antagonist

Uses:

Labeled Uses^{1,2,3}: Prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure.

Unlabeled Uses: None listed

Mechanism of Action^{1,2,3}: Ulipristal acetate acts selectively on the human progesterone receptor and prevents progesterone from binding. When administered before ovulation, it postpones follicular rupture and therefore inhibits or delays ovulation. Additionally, ulipristal acetate alters the endometrium, which contributes to its efficacy by affecting implantation.

Pharmacokinetics:

Absorption^{1,2,3}:

Healthy Female Volunteers under Fasting Conditions

	Ulipristal acetate	Monodemethyl-ulipristal acetate (active metabolite)
T _{max}	0.9 hr (Range: 0.5 to 2 hr).	1.00 hr (Range: 0.8 – 2.0)
V _d	Not reported	Not reported
t _{1/2}	32 hr (+/- 6.3 hr)	27 hr (+/- 6.9 hr)
Clearance	Not reported	Not reported
Protein binding	Greater than 94% to plasma proteins, including HDL, alpha-1-acid glycoprotein, and albumin	Not reported
Bioavailability	Not reported	Not reported

Metabolism^{1,2,3}: Ulipristal acetate is metabolized predominately via CYP3A4-mediated pathway to mono- and di-demethylated metabolites. Monodemethyl-ulipristal acetate is active.

Elimination: Not reported

Efficacy:

Creinin MD et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. *Obstet Gynecol.* 2006 Nov;108(5):1089-97⁴.

Study Design: Multicenter, double-blind, active-controlled, parallel-group non-inferiority study design

Description of Study: *Methods:* One thousand six hundred seventy two women who were at least 18 years of age, not pregnant, not breast-feeding within the past 2 months, did not use an IUD, or male or female sterilization as a method of contraception were enrolled in this study. The women also had to have had at least 2 menses since the last use of oral contraceptives. Patients presenting within 72 hours of intercourse were randomized to receive either 50mg CDB-2914 plus an identical placebo capsule 12 hours later, or they could receive 0.75 mg levonorgestrel plus another 0.75mg levonorgestrel 12 hours later. The first dose was taken under direct supervision. A follow-up visit was conducted 5-7 days after expected onset of next menses. ***Outcome Results:*** In the modified intention-to-treat population, 12 pregnancies (1.5%) were observed in the CDB-2914 group (95% CI 0.7-2.4) and 14 pregnancies (1.8%) were recorded in the levonorgestrel group (95% CI 0.9-2.7), (ARR: -0.3%, p=0.003). There were several adverse effects reported including nausea, vomiting, headache, dizziness, fatigue, breast tenderness, lower abdominal pain, and diarrhea. The only adverse event which was statistically significantly different between the CDB-2914 and levonorgestrel was nausea (3.7% vs 3.1%, p=0.03).

Limitations: The second tablet of either levonorgestrel or placebo could have potentially been taken outside the 72 hour window. Since the second tablet was given to the women to take unobserved, they may not have taken the dose at the correct time or at all. A single-dose levonorgestrel product would have provided a better comparison against the ulipristal acetate. Women may have been unsure as to what was the day of their last period, potentially confounding the data on dose timing during menstrual cycle.

Conclusion: CDB-2914 appears to be just as effective as levonorgestrel in preventing pregnancy when taken within 72 hours of sexual intercourse. Further studies are needed to be able to extrapolate the results to the general population.

Glazier, AF et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *Lancet.* 2010 Feb 13;375(9714):555-62. Epub 2010 Jan 29⁵.

Study Design: Multicenter, single-blind, active-controlled, parallel-group non-inferiority study and retrospective meta-analysis

Description of Study: *Methods:* Two thousand two hundred twenty one women who were not pregnant, breast-feeding, sterilized, fitted with an IUD, had a sterilized partner,

or taking hormonal contraception were enrolled and randomized in this study. Patients either received ulipristal acetate 30mg or levonorgestrel 1.5mg. Each patient received follow-up 5-7 days after expected menses. If menses occurred and the patient received negative results from a pregnancy test, participation in the study ended. Women who had negative pregnancy tests but did not menstruate were contacted every 2 weeks and periodic pregnancy tests were performed until 60 days had passed. Analysis of the data from this trial was based on an efficacy-evaluable population for primary and secondary outcomes. *Outcome Results:* The primary endpoint in this study was the rate of pregnancy in women who received oral emergency contraceptives within 72 hours of unprotected sex. There were 15 pregnancies (1.8%, 95% CI 1.0-3.0) in the 844 women in the ulipristal acetate group, and 22 (2.6%, 95% CI 1.7 – 3.9) in the levonorgestrel group [OR 0.68, 95% CI 0.35-1.31]. The secondary endpoint was the rate of pregnancy when women received oral emergency contraceptives within 120 hours of unprotected sex. The current study found that 15/941 (1.6%) women became pregnant after taking ulipristal acetate within 120 hours of sexual intercourse, and 25/958 (2.6%) became pregnant after taking levonorgestrel with 120 hours of sexual intercourse (OR: 0.57, 95% CI 0.29-1.09, p=0.091). There were no significant differences in adverse effects reported in this study. The most frequent adverse effects reported were headache, dysmenorrhea, nausea, abdominal pain, fatigue, dizziness, and back pain.

Limitations: This study was funded by HRA Pharma. Several of the authors consult for this company, and one of the authors owns equity in the company. These conflicts of interest may have influenced the manner in which the data were reported. The study protocol mentions that women who presented after 72 hours had the option of receiving an IUD. No data are reported to state whether or not any women chose this option. About half of the women in the study had previously used an emergency contraceptive; this could have caused some unblinding if the women recognized the previous tablet. Also, this study was only single-blinded, so some bias could have been introduced.

Conclusion: The authors concluded that ulipristal acetate is a good alternative to levonorgestrel for emergency contraception up to 5 days after intercourse. The meta-analysis did show a statistically significant difference in the number of pregnancies using ulipristal acetate versus levonorgestrel for emergency contraception (1.6% vs 2.2%, p=0.025). Further study is needed to be able to extrapolate the results from this study to the general population.

Fine P, Mathé H, Ginde S, Cullins V, Morfesis J, and Gainer E. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. *Obstet Gynecol.* 2010 Feb;115(2 Pt 1):257-63⁶.

Study Design: Multicenter, prospective, open-label study design

Description of Study: *Methods:* A total of 1,533 women who had regular menstrual cycles, and not currently taking hormonal contraceptives, pregnant, breast-feeding, IUD, tubal ligation, or had a partner with a vasectomy was enrolled in the study. The women presented to the clinic 48-120 hours after unprotected intercourse. At the first visit, the women received a single dose of 30mg ulipristal acetate. They also got a high-sensitivity pregnancy test and a blood sample was taken to evaluate serum B-hCG. A follow-up visit occurred 5-7 days after expected onset of menses, when another pregnancy test was given. If no menses had occurred and the pregnancy test was negative, the protocol was repeated after 1 week, then every 2 weeks as necessary for up to 60 days. *Outcome Results:* The primary endpoint of this study was the pregnancy rate. Overall, for women presenting between 48-120 hours after intercourse, the observed pregnancy rate was 2.1% (95% CI 1.4-3.1) in the modified intention-to-treat population. Since the expected pregnancy rate using the pooled recognizable set of conception possibilities was 5.5%, the percent of pregnancies prevented was 62.3% (95% CI 41.9-75.6). The most commonly reported adverse events were headache, nausea, abdominal pain, and dysmenorrhea.

Limitations: Two of the authors work for HRA Pharma, the company which funded this study. This may have introduced bias in the way the authors reported data. Confidence intervals for some of the evaluated parameters were quite large, which may limit clinical predictability of efficacy in general patient populations. This study was an open-label design, which could have introduced bias from both patients and investigators. Also, pregnancy predictions were made using a pooled analysis. A simultaneous active control would have been a better comparison as to how many women would actually become pregnant.

Conclusion: This study shows that ulipristal acetate is efficacious in reducing the risk of pregnancy when taken between 48-120 hours of sexual intercourse when compared to the expected pregnancy rate. Side effects are generally mild or moderate, and should not prevent women from using this method of emergency contraception.

Contraindications^{1,2,3,4,5,6}:

Pregnancy: Known or suspected pregnancy is a contraindication of the use of ulipristal acetate. Ulipristal acetate is not indicated for the termination of an existing pregnancy.

Precautions^{1, 2,3}:

Ectopic pregnancy: Ulipristal acetate may increase the risk for ectopic pregnancy. A history of ectopic pregnancy is not a contraindication to use of this emergency contraceptive method. Healthcare providers, however, should consider the possibility of ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking ulipristal acetate. A follow-up physical or pelvic examination is

recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking ulipristal acetate.

Repeated Use: Ulipristal acetate is for occasional use as an emergency contraceptive. It should not replace a regular method of contraception. Repeated use of ulipristal acetate within the same menstrual cycle is not recommended, as safety and efficacy of repeat use within the same cycle has not been evaluated.

Fertility Following Use: Fertility is likely to rapidly return following treatment with ulipristal acetate for emergency contraception; therefore, routine contraception should be continued or initiated as soon as possible following use of ulipristal acetate to ensure ongoing prevention of pregnancy. After use of ulipristal acetate, a reliable barrier method of contraception should be used with subsequent acts of intercourse that occur in that same menstrual cycle.

Effect on Menstrual Cycle: After ulipristal acetate intake, menses sometimes occur earlier or later than expected by a few days. If there is a delay in the onset of expected menses beyond 1 week, rule out pregnancy.

Sexually Transmitted Infections/HIV: Ulipristal acetate does not protect against HIV infection (AIDS) or other sexually transmitted infections (STIs).

Adverse Effects^{1,2,3,5}:

Neurologic:

Headache (18% to 19%)

Dizziness (5%)

Gastrointestinal:

Abdominal pain (8% to 15%)

Nausea (12% to 13%)

Reproductive:

Bleeding between periods (9%)

Dysmenorrhea (7% to 13%)

Other:

Fatigue (5% to 6%)

Drug Interactions^{1,2,3}:

Inducers of CYP 3A4

Drugs or herbals that induce CYP 3A4 may decrease the plasma concentrations of ulipristal acetate and may decrease its effectiveness. Examples of these are:

barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, phenytoin, primidone, rifampin, St. John's Wort, and topiramate

Inhibitors of CYP 3A4

CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma concentrations of ulipristal acetate.

Oral Contraceptives

While there are no data about use of ulipristal acetate with regular hormonal contraceptives, due to its high affinity binding to the progesterone receptor, use of ulipristal acetate may reduce the contraceptive action of regular hormonal contraceptive methods.

Dosing/Administration^{1,2,3,5,6}:

Adult dosing:

Females: 30 mg orally as soon as possible within 120 hours (5 days) of unprotected intercourse or a known or suspected contraceptive failure. If vomiting occurs within 3 hours, consider repeating dose. Ulipristal acetate can be taken with or without food.

Males: Ulipristal acetate is not intended for use by males.

Pediatric dosing

Post-pubertal females: 30 mg orally as soon as possible within 120 hours (5 days) of unprotected intercourse or a known or suspected contraceptive failure. If vomiting occurs within 3 hours, consider repeating dose.

Pre-pubertal females: Use of ulipristal acetate before menarche is not indicated.

Geriatric dosing:

This product is not intended for use in postmenopausal women.

Hepatic impairment:

No studies have been conducted to evaluate the effect of liver disease on the disposition of ulipristal acetate.

Renal impairment:

No studies have been conducted to evaluate the effect of kidney disease on the disposition of ulipristal acetate.

Use in Special Populations^{1,2,3}:

Pregnancy: Ulipristal acetate is pregnancy category X. Pregnancy is a contraindication to taking ulipristal acetate. There are no adequate and well controlled studies in pregnant women.

Lactation: It is not known if ulipristal acetate is excreted in human milk. However, ulipristal acetate is detected in milk of lactating rats. Use of ulipristal acetate by breastfeeding women is not recommended.

Race: No difference in efficacy and safety was observed for women of different races in clinical studies.

Use in special circumstances^{1,2,3}:

Overdosage: Experience with ulipristal acetate overdose is limited. In a clinical study, single doses equivalent to up to four times the usual dose of ulipristal acetate were administered to a limited number of subjects without any adverse reactions.

Conclusion: Ulipristal acetate appears to be at least as safe and effective as levonorgestrel, the currently available non-prescription emergency contraceptive. The side effects of ulipristal acetate appear to be mild to moderate and comparable to levonorgestrel. Studies to determine the effect of concurrently used oral contraceptives and ulipristal acetate still need to be conducted. Though ulipristal acetate has shown some efficacy if taken up to 120 hours after intercourse, the drug should be taken as soon as possible. Ulipristal acetate requires a prescription at this time, which may limit the availability of the drug when compared to levonorgestrel. Based on this information, women should use the most readily available emergency contraceptive (generally levonorgestrel) unless they are presenting to the pharmacy or clinic more than 72 hours after intercourse. In this case, ulipristal acetate appears to be a clinically useful emergency contraceptive agent up to 120 hours after sexual intercourse.

Recommended References:

1. Ella® [package insert]. Morristown, NJ: Watson Pharma, Inc; 2010.
2. Ulipristal acetate. In DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed October 6, 2010.
3. Ulipristal acetate Oral. Facts & Comparisons 4.0 Online [Internet database]. Wolters Kluwer. Available at: <http://online.factsandcomparisons.com>. Accessed October 12, 2010.
4. Creinin MD et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. *Obstet Gynecol.* 2006 Nov;108(5):1089-97.

5. Glasier, AF et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *Lancet*. 2010 Feb 13;375(9714):555-62. Epub 2010 Jan 29.
6. Fine P, Mathé H, Ginde S, Cullins V, Morfesis J, and Gainer E. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. *Obstet Gynecol*. 2010 Feb;115(2 Pt 1):257-63.

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