Ulipristal Acetate (ella)
A Selective Progesterone Receptor Modulator
For Emergency Contraception

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INTRODUCTION

In the U.S., it is estimated that one-half of the six million pregnancies that occur each year are unplanned or unexpected. Despite the widespread use of various contraceptive methods, including hormonal contraceptive tablets and condoms, these methods remain imperfect. Inadequate contraceptive use or failure of a contraceptive method, in addition to unprotected sexual intercourse, may contribute to the incidence of unintended pregnancies. According to the Centers for Disease Control and Prevention (CDC), an estimated 1.21 million abortions were reported in 2005 in the U.S.2 Easier access to postcoital or emergency contraception (EC) might help to reduce the incidence of unintended pregnancy and abortion.

Recent data indicate that women are increasingly seeking EC use, with 4% reporting having used it at least once in 2002 and 10% reporting use between 2006 and 2008. A variety of EC methods, including oral medications and a copper intrauterine device (IUD)—which may be inserted up to five days after unprotected intercourse—are currently available. Although sometimes referred to as the “morning-after pill,” this moniker is misleading; the hormonal EC tablet containing levonorgestrel (Plan B One-Step, Barr; Next Choice, Watson Laboratories) is approved for use within 72 hours of unprotected intercourse.4,5

In August 2010, ulipristal acetate (ella, Laboratoire HRA Pharma/Watson Laboratories) was the first agent in the novel selective progesterone receptor modulator class to gain the FDA’s approval for use as an oral EC tablet in the U.S.6 The drug is used to prevent unintended pregnancy for up to five days after unprotected intercourse or contraceptive failure.7

Table 1 presents a summary of the differences between ulipristal acetate and levonorgestrel.4-7

PHARMACOLOGY

The female menstrual cycle comprises three distinct phases: follicular, ovulatory, and luteal. The first day of menstrual bleeding marks the start of the follicular phase, in which the production of follicle-stimulating hormone (FSH) by the pituitary gland increases and stimulates the growth of ovarian follicle cells. One follicle begins to predominate and secretes estrogen to support its development. The ovulatory phase begins when the midcycle surge of luteinizing hormone (LH) occurs and the follicle ruptures, releasing an egg cell.

During the luteal phase, the follicle closes to form the corpus luteum, which stimulates the production of progesterone. Increases in progesterone and estrogen during this phase allow for the preparation of the endometrium for implantation if fertilization of the egg occurs. Progesterone causes thickening of the endometrium and alters the viscosity of cervical mucus to block bacteria and sperm. Released continuously, progesterone aids in nourishing the embryo until the fetus is able to produce hormones independently.8,9

Ulipristal acetate exerts its pharmacological activity by binding to the body’s progesterone receptors to produce an anti-progesterone contraceptive effect on the ovary (by suppressing or delaying ovulation) and on the endometrium (by decreasing endometrial thickness). These effects vary according to the timing of drug administration during the menstrual cycle.10 Progesterone is crucial for pregnancy to occur and for sustaining the pregnancy by preparing the endometrium for implantation of the fertilized egg.10

Ulipristal acetate binds to the progesterone receptor and blocks the hormone’s effects. To achieve improved specificity for the progesterone receptor, ulipristal acetate was developed to be a derivative of 19-norprogesterone. It possesses the ability to inhibit or delay ovulation, ultimately preventing pregnancy within 120 hours of unprotected intercourse or suspected contraceptive failure. The medication’s effects may vary, depending on the dose and phase of the menstrual cycle during which it is taken.11

Administering ulipristal acetate before ovulation causes delayed follicle development and release, probably a result of suppression of estradiol levels. If the EC drug is taken during the LH peak, follicular rupture and ovum release may also be delayed.11 During the latter part of the menstrual cycle, ulipristal acetate’s effect may be attributed to its ability to decrease endometrial thickness.6

In addition to its effects on human progesterone receptors, ulipristal acetate binds to glucocorticoid and androgen receptors. However, its capacity as an antagonist in binding to these receptors is markedly lower than its anti-progesteroidal activity. Anti-glucocorticoid and anti-androgen activities were observed at doses 50-fold greater than that necessary for an anti-progestin effect, indicating that ulipristal acetate is a progesterone receptor modulator with reduced anti-glucocorticoid activity.11

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**Table 1 Ulipristal Acetate and Levonorgestrel, Product Comparison**

<table>
<thead>
<tr>
<th></th>
<th>Levonorgestrel&lt;sup&gt;4,5&lt;/sup&gt;</th>
<th>Ulipristal Acetate&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Barr, Watson Pharma</td>
<td>Watson Pharma</td>
</tr>
<tr>
<td><strong>Year of approval</strong></td>
<td>2006, as Plan B; 2009, as Plan B One-Step and Next Choice</td>
<td>2010, as ella</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>Synthetic progestogen</td>
<td>Selective progesterone receptor modulator</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Prevents ovulation by modifying the pathway of sperm; affects the endometrium and implantation</td>
<td>Prevents or suspends ovulation by binding to the progesterone receptor; affects endometrium and implantation</td>
</tr>
<tr>
<td><strong>Dosage and administration</strong></td>
<td>1.5-mg oral tablet (Plan B One-Step) as a single dose, taken after unprotected intercourse as soon as possible (and within 72 hours) or 0.75-mg oral tablet (Next Choice) taken after unprotected intercourse as soon as possible, with a second tablet taken 12 hours after the first</td>
<td>30-mg oral tablet as a single-dose, taken after unprotected intercourse as soon as possible (and within 120 hours)</td>
</tr>
<tr>
<td><strong>Adverse reactions</strong></td>
<td>Heavier menstrual bleeding, nausea, abdominal pain, fatigue, headache, dizziness, breast tenderness, delayed menses</td>
<td>Headache, nausea, abdominal pain, dysmenorrhea, fatigue, dizziness</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Pregnancy</td>
<td>Pregnancy</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Over-the-counter agent for women 17 years of age or older (prescription required for women younger than age 17)</td>
<td>Prescription only (health care professionals must perform pregnancy test to rule out pregnancy)</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$40.62 for 1.5-mg tablet (Plan B One-Step) or $35.10 for two 0.75-mg tablets (Next Choice)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>$42.90 per tablet&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cost information from Red Book<sup>7</sup>. Data from package inserts for Plan B One-Step<sup>4</sup>, Next Choice<sup>5</sup>, and ella<sup>6</sup>.

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**PHARMACOKINETICS**

The parameters of absorption, distribution, metabolism, and excretion of ulipristal acetate are described as follows.

**Absorption and Distribution**

When administered by mouth at a dose of 30 mg, ulipristal acetate is rapidly absorbed. The maximum mean serum concentration (C<sub>max</sub>) ± the standard deviation (SD) of 176 ± 89 ng/mL is observed at approximately one hour. Its active metabolite, mono-demethyl-ulipristal acetate, has a C<sub>max</sub> of 69 ± 26 ng/mL, which is also exhibited at about one hour. Taken after a high-fat meal, the drug's C<sub>max</sub> is decreased by 40% to 45%, the time to maximum concentration (T<sub>max</sub>) is delayed by three hours, and the area-under-the-drug concentration (AUC) curve is increased by 20% to 25%, compared with administration during the fasting state. These differences in absorption, however, are not expected to be clinically relevant; thus, ulipristal acetate can be taken with or without food.<sup>6</sup>

The drug exhibits high plasma protein binding to albumin, alpha<sub>1</sub>-acid glycoprotein, and high-density lipoprotein-Cholesterol (HDL-C). Its effects in patients with altered plasma protein levels is unknown.<sup>11</sup>

**Metabolism**

Ulipristal acetate is metabolized to mono-demethylated and di-demethylated metabolites. Metabolism occurs predominantly by the cytochrome P450 (CYP) 3A4 hepatic isoenzyme and, to a lesser extent, by CYP 1A2.<sup>4,5</sup> Although the mono-demethylated metabolite is pharmacologically active, the di-demethylated metabolite has no clinical activity.

The half-life of the drug in plasma, following a single dose of 30 mg, is approximately 32.4 ± 6.3 hours.<sup>6</sup> In pharmacokinetic and population studies, ulipristal acetate has not shown any significant variations in women of different races; however, the drug is not recommended for breast-feeding or postmenopausal women.<sup>5</sup> The concomitant administration of medicinal products that tend to increase gastric pH may also decrease the drug’s efficacy.<sup>11</sup>

**Excretion**

No studies have been conducted to evaluate the effect of hepatic and renal disease on the disposition of ulipristal acetate. Women with severe renal or hepatic impairment should not receive this drug because of the lack of data regarding safety and efficacy in these patient populations.

**CLINICAL EFFICACY**

The safety and efficacy of ulipristal acetate for use in emergency contraception (EC) have been evaluated in four clinical trials; two of these are considered to be pivotal phase 3 trials.<sup>12,13</sup> Of note, the presently approved 30-mg dose and the micronized tablet formulation were used in these two studies; a 50-mg gelatin capsule was used in the other two phase 2 and 3 studies.

**Fine et al.**<sup>12</sup>

A prospective, multicenter, open-label study was conducted at 45 Planned Parenthood clinics in the U.S. to assess the efficacy of ulipristal acetate. A single 30-mg tablet was administered as EC 48 to 120 hours after unprotected intercourse. Women were eligible for enrollment if they were 18 years of age; had a regular menstrual cycle (between 24 and 35 ± 5 days in length); were not currently using hormonal contraceptives; and were willing to use a barrier contraceptive method instead of hormonal tablets until
the study’s completion. Women were excluded from the study if they were pregnant; were breast-feeding; were using an IUD; had undergone tubal ligation or had a partner with a vasectomy; or reported an ambiguous menstrual history.

At the baseline evaluation, a high-sensitivity urine pregnancy test was performed. A blood sample was taken and stored to be used for a serum human chorionic gonadotropin (β-hCG) test. The β-hCG test was performed to exclude pre-existing pregnancy that might have gone undetected by the urine test if pregnancy occurred during the study. Throughout the study, patients were required to keep daily diaries and record any occurrences of intercourse, the use of contraception, intermenstrual bleeding or spotting, the concomitant use of medications, and adverse effects (AEs).

Urine tests for pregnancy were performed on two or three different occasions: at enrollment; five to seven days after the expected onset of menses; and, if necessary, 12 to 14 days after the expected onset of menses if menses had not yet occurred. If the test result was positive, pregnancy was verified by a serum β-hCG test. The pre-treatment blood sample was also assayed for β-hCG at that time to determine the possibility of a false-negative result on the urine-based test at trial enrollment.

For women whose test result was negative and who had begun to menstruate, their participation in the trial was completed. For women whose test result was negative and who had not experienced menses, follow-up and pregnancy tests were continued each week until menses occurred. Women whose test result was negative after 60 days were evaluated for secondary amenorrhea.

The primary efficacy endpoint was the resulting pregnancy rate, defined as the number of pregnancies occurring after administration of ulipristal acetate, divided by the number of treated patients. Of 1,623 patients requesting EC, 1,533 women were included in the intent-to-treat (ITT) population; 1,241 women were included in the modified intent-to-treat (mITT) population, which was used to evaluate the primary efficacy endpoint. Patients were included in the primary efficacy (mITT) population if they were not excluded for these reasons: age older than 35 years; previous enrollment; failure to attend follow-up; and a pregnancy considered by the data safety monitoring board to be unlikely to be unrelated to EC failure.

The main secondary endpoint was to compare the upper limit of the 95% confidence interval (CI) of the observed pregnancy rate with a clinical irrelevance threshold, defined as 4%. Other secondary endpoints include the proportion of pregnancies prevented and the analysis of the trend in pregnancy rates over time using logistic regression.

Of the 1,241 women in the primary efficacy population, 26 pregnancies occurred, resulting in a 2.1% pregnancy rate (95% CI, 1.4%–3.1%), compared with the 5.3% expected pregnancy rate in the absence of EC. The observed pregnancy rate of 2.1% was lower than the upper limit of the 95% CI of 3.1% and also below the clinical irrelevance threshold of 4%; thus, the resulting pregnancy rate met the defined primary efficacy endpoint and the efficacy of the study drug was confirmed.

In the ITT population (N = 1,533), the observed pregnancy rate was 1.9% (95% CI, 1.3%–2.8%), compared with an expected pregnancy rate of 5.7%. Overall, the use of ulipristal acetate prevented 62.3% of pregnancies (95% CI, 41.9%–75.6%), with no change in efficacy demonstrated over time. Observed pregnancy rates were 2.3%, 2.1%, and 1.3%, respectively, when the drug was administered 48 to 72 hours, more than 72 to 96 hours, and more than 96 to 120 hours after unprotected intercourse. However, the statistic of 62.3% could be inaccurate; it might have been higher, because 14 of the 26 observed pregnancies resulted from unprotected intercourse occurring outside of the presumed window of fertility.

In the ITT population, 2,232 AEs were documented among 876 women receiving ulipristal acetate. The incidence rate of AEs most likely related to the study drug was 49.6%. No participants withdrew from the study because of an adverse reaction. The most commonly reported AEs were headache (9.3%), nausea (9.2%), and abdominal pain (6.8%); most of these AEs were mild or moderate in severity. Other AEs included a longer menstrual cycle, from a mean of 29 days at baseline to 31.8 days at the trial’s end; 1,256 women (9.2%) reported delayed onset of menses by seven days or more after treatment, and 94 patients (7%) experienced delayed menses by 15 days or more.

Intermenstrual bleeding was reported by 134 women (8.7%) following treatment; 51 women (3.3%) were documented as having had intermenstrual bleeding before enrollment, and 91.8% of the bleeding episodes were described as spotting with no clinically significant effect on biochemical parameters.

The investigators concluded that a single 30-mg dose of ulipristal acetate was effective as EC when given within 48 to 120 hours of unprotected intercourse compared with no intervention. The drug was well tolerated, with a clear benefit as a hormonal method of EC.

Glasier et al.13

To compare the safety and efficacy of ulipristal acetate (ella) with levonorgestrel (Plan B One Step), the Glasier team conducted a randomized, multicenter, multinational, single-blind, non-inferiority trial at 35 family-planning clinics in the United Kingdom, Ireland, and the U.S. Women who requested EC within 120 hours of unprotected intercourse and who were at least 16 years of age (for United Kingdom and Ireland clinics) and 18 years of age (for sites in the U.S.) were eligible for trial enrollment. Women were excluded if they were pregnant, were breast-feeding, were currently using an IUD or a hormonal contraceptive, had undergone sterilization, or had a partner who had undergone a vasectomy.

Upon enrollment, a urine pregnancy test was performed and blood sample was taken and stored. The study was considered to be single-blinded; patients did not know the contents of the medication, but those administering the drug and the investigators were aware of treatment distributions based on the drug’s packaging and tablet shape.

A Web-based electronic case record system was used to assign the women (N = 2,221) to receive either a one-time 1.5-mg dose of levonorgestrel (Plan B One-Step) (n = 1,117) or ulipristal acetate (ella) 30 mg (n = 1,104). Patients were required to keep a daily record of any incident of sexual intercourse, the use of contraception, vaginal bleeding, the concomitant use of other medications, and AEs.
A follow-up evaluation was scheduled five to seven days after the expected onset of menses. During this time, another pregnancy test was performed. If the result was negative and menses occurred, the study was considered to be complete. If the result was negative but menses did not occur, further follow-up and periodic pregnancy tests were performed. This procedure was continued until menses returned or until 60 days elapsed without menses; at that point, the cause of the amenorrhea was investigated further. If the test result was positive, a serum β-hCG assay was conducted to validate the findings. A pretreatment serum test was also performed to verify whether the pregnancy had occurred before the patient received the drug.

The primary efficacy endpoint was the rate of pregnancy in women who were treated within 72 hours of unprotected intercourse. The rate of pregnancy for those who took the study drug within 120 hours of unprotected intercourse was considered to be a secondary endpoint. Participants were excluded from the efficacy-evaluable population (mITT = 1,899) if they did not receive a follow-up assessment; if they were 36 years of age or older; if they had been enrolled previously; if their follow-up pregnancy status was unknown; or if a pregnancy was deemed unrelated to EC failure.

In the ITT population, 50 pregnancies were recorded (20 in the ulipristal acetate groups, 30 in the levonorgestrel groups) among the 2,221 enrolled women. In the efficacy-evaluable population, administration of the EC drug within 72 hours of unprotected intercourse resulted in 37 pregnancies. Of that group, 22 women (2.6%; 95% CI, 1.7–3.9) were among the 852 receiving levonorgestrel, and 15 women (1.8%; 95% CI, 1.0–3.0) were among the 844 receiving ulipristal acetate. This finding was not statistically significant (odds ratio, 0.68; 95% CI, 0.35–1.31).

Of the participants who were treated within 72 to 120 hours after unprotected intercourse (N = 203), three pregnancies occurred, all in the levonorgestrel group. Within this time period, considerably more pregnancies were prevented with ulipristal acetate than with levonorgestrel (P = 0.037). In both study groups, the pregnancy rate with ulipristal acetate (1.8%) was significantly lower than the expected rate (5.5%) (P = 0.001). The pregnancy rate with levonorgestrel was 2.6%; the expected rate had been 5.4% (P = 0.001).

Adverse effects (AEs) were observed in 597 women (54%) taking ulipristal acetate and in 626 women (56%) receiving levonorgestrel. For both study drugs, 1,414 reactions (94%) in the ulipristal acetate group and 1,531 reactions (94%) in the levonorgestrel group were regarded as mild or moderate; headache, dysmenorrhea, and nausea were the most commonly reported AEs. In the two groups, more serious AEs were dizziness with ulipristal acetate and molar pregnancy with levonorgestrel.

Menses occurred at a mean of 2.1 days later (SD, 8.2) in women receiving ulipristal acetate and 1.2 days (SD, 7.9) earlier in the women receiving levonorgestrel (P = 0.001). Ulipristal acetate was associated with a lower pregnancy rate than levonorgestrel within 24, 72, and 120 hours of administration after unprotected intercourse. The Gläser authors concluded that ulipristal acetate was non-inferior to levonorgestrel and was tolerated to a similar level.

SAFETY AND TOLERABILITY

Ulipristal acetate is generally well tolerated, and its AEs and risks are considered to be no more severe than those of levonorgestrel.11,12 In clinical trials, the most prevalent AEs included headache, nausea, fatigue, dizziness, abdominal pain, and dysmenorrhea; these AEs were considered to be mild to moderate in severity and spontaneously resolved.11,12 The use of ulipristal acetate may also cause a delayed onset of the next expected menstrual period, although this effect is usually transient; the menstrual cycle typically returns to normal for subsequent cycles.

CONTRAINdications AND PRECAUTIONs

Classified as a Pregnancy Category X drug, ulipristal acetate is contraindicated in patients who are pregnant or who are unsure of their pregnancy status. Although it is not known whether the drug induces fetal damage when taken during pregnancy, women should still be counseled and warned of possible fetal harm. Because of the unknown fetal effects, this drug should not be taken by nursing mothers. Although ulipristal acetate has been studied for use in women as young as 16 years of age, it is currently approved for use in patients 18 years of age and older. It is not indicated for use before menarche or in postmenopausal women.6

DOSAGE AND ADMINISTRATION

The recommended dosage of ulipristal acetate is a single 30-mg oral tablet, taken after unprotected intercourse or contraceptive failure. The drug should be taken as soon as possible and within five days (120 hours) of the incident. The tablet may be taken regardless of food intake or time of menstrual cycle. If vomiting occurs within three hours after administration, it may be necessary to take a second tablet.6 Ulipristal acetate is not intended for use as a method of routine hormonal contraception, and it does not protect against sexually transmitted disease or transmission of HIV infection.

DRUG INTERACTIONS

In vitro studies indicate that ulipristal acetate is a substrate metabolized predominantly by the CYP 3A4 isoenzyme. Inducing this isoenzyme may decrease the drug’s activity by reducing its plasma concentrations. Therefore, although in vivo data are not available, it is presumed that taking ulipristal acetate with medications that tend to induce CYP 3A4 results in decreased efficacy of the EC product.

The drug’s effectiveness may be reduced when it is taken concomitantly with barbiturates, bosentan (Tracleer, Actelion), carbamazepine (Tegretol, Novartis; Carbactol, Shire), felbamate (Felbatol, Wallace), griseofulvin (Grifulvin, Ortho; Fulvicin U/F, Schering), oxcarbazepine (Trileptal, Novartis), phenytoin (Dilantin, Pfizer), rifampin, St. John’s Wort, or topiramate (Topamax, Ortho-McNeil). In contrast, its use in conjunction with any product that tends to inhibit CYP 3A4, such as Janssen’s itraconazole (Sporanox) or ketoconazole (Nizoral), may result in increased plasma concentrations of the EC drug.6

Alterations in gastric pH may also reduce absorption and plasma levels of ulipristal acetate. Patients should avoid the concomitant use of acid-suppressive drugs, such as proton pump inhibitors,
histamine₂-receptor antagonists, and antacids. For women who use hormonal birth control and who take ulipristal acetate, there is a theoretical risk that the EC drug may reduce the efficacy of the other contraceptive methods for the duration of the menstrual cycle. After taking ulipristal acetate, women should use a barrier method of contraception until the menses has resumed.6,11

COST AND ECONOMIC IMPACT

Considering the burden of cost of unwanted or unplanned pregnancies on society, the price of emergency contraception (EC) products containing either levonorgestrel or ulipristal acetate is considered nominal (see Table 1).4–7 A single 30-mg tablet of ulipristal acetate has an average wholesale price of $42.90 and patients can purchase this product for between $50 and $55 per dose.7 In addition to the cost of the product itself, women must obtain a prescription from a Planned Parenthood clinic or a primary health care provider, resulting in another cost for the office visit.

CONCLUSION

Unplanned or unintended pregnancies account for about half of all pregnancies in the U.S. each year. If contraceptive failure, sexual assault, or unprotected intercourse has occurred, ulipristal acetate (ella) may serve a specific need, particularly for women who are unaware of the availability of emergency contraception or who delay seeking medical attention. The availability of a noninvasive oral tablet that maintains efficacy in preventing pregnancy for up to five days after unprotected intercourse may offer another option for women who desire to avoid pregnancy. For P&T committees reviewing ulipristal acetate for use in ambulatory-care clinics or for victims of sexual assault, this product's expanded window of efficacy in preventing unintended pregnancy may make it a desirable addition to the formulary. Clinical trials evaluating the use of ulipristal acetate for the treatment of uterine fibroids are currently ongoing.

REFERENCES