

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022474Orig1s007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ella safely and effectively. See full prescribing information for ella.

ELLA (ulipristal acetate) tablet

Initial U.S. Approval: 2010

-----RECENT MAJOR CHANGES-----

- Warnings and Precautions, Existing Pregnancy (5.1) 8/2014
- Warnings and Precautions, CYP3A4 Inducers (5.4) 6/2014
- Warning and Precautions, Fertility following use (5.5) 3/2015

-----INDICATIONS AND USAGE-----

ella is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. ella is not intended for routine use as a contraceptive. (1)

-----DOSAGE AND ADMINISTRATION-----

- One tablet taken orally as soon as possible, within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure. (2)
- The tablet can be taken with or without food. (2)

-----DOSAGE FORMS AND STRENGTHS-----

- 30 mg tablet (3)

-----CONTRAINDICATIONS-----

- Known or suspected pregnancy (4)

-----WARNINGS AND PRECAUTIONS-----

- ella is not indicated for termination of an existing pregnancy. Exclude pregnancy before administering. (5.1)

- Subsequent acts of intercourse should be protected by a reliable barrier method until next menstrual period. If a woman wishes to use hormonal contraception, she should do so no sooner than 5 days after intake of ella. (5.5)
- Ectopic pregnancy: Women who become pregnant or complain of lower abdominal pain after taking ella should be evaluated for ectopic pregnancy. (5.2)
- Effect on menstrual cycle: ella may alter the next expected menses. If menses is delayed beyond 1 week, pregnancy should be ruled out. (5.6)
- ella does not protect against STI/HIV. (5.7)

-----ADVERSE REACTIONS-----

The most common adverse reactions ($\geq 5\%$) in the clinical trials were headache (18%), abdominal pain (12%), nausea (12%), dysmenorrhea (9%), fatigue (6%) and dizziness (5%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Afaxys, Inc. at 1-855-888-2467 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Drugs or herbal products that induce CYP3A4 decrease the effectiveness of ella. (7)

-----USE IN SPECIFIC POPULATIONS-----

- Nursing mothers: ella is not recommended for use by breastfeeding women. (8.3)
- ella is not intended for use in premenarcheal (8.4) or postmenopausal women. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA Approved Patient Labeling

Revised: 3/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ella is a progesterone agonist/antagonist emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure. **ella** is not intended for routine use as a contraceptive.

2 DOSAGE AND ADMINISTRATION

Instruct patients to take one tablet orally as soon as possible within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure.

The tablet can be taken with or without food.

If vomiting occurs within 3 hours of **ella** intake, consideration should be given to repeating the dose.

ella can be taken at any time during the menstrual cycle.

3 DOSAGE FORMS AND STRENGTHS

The **ella** tablet is supplied as a white to off-white, round, curved tablet containing 30 mg of ulipristal acetate and is marked “ella” on both sides.

4 CONTRAINDICATIONS

ella is contraindicated for use in the case of known or suspected pregnancy. The risks to a fetus when **ella** is administered to a pregnant woman are unknown. If this drug is inadvertently used during pregnancy, the woman should be apprised of the potential hazard to the fetus. [See *Use in Specific Populations (8.1)*.]

5 WARNINGS AND PRECAUTIONS

5.1 Existing Pregnancy

ella is not indicated for termination of an existing pregnancy. Pregnancy should be excluded before prescribing **ella**. If pregnancy cannot be excluded on the basis of history and/or physical examination, pregnancy testing should be performed. 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 **ella**.

A web-based study has been established to collect information on the pregnancy outcomes of women who inadvertently receive **ella** during the cycle in which pregnancy started or at anytime during pregnancy.

Enroll your patient by completing the forms available at www.ellipse2.com where voluntary reports from health care providers or consumers are received.

5.2 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 **ella**. 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 **ella**.

5.3 Repeated Use

ella is for occasional use as an emergency contraceptive. It should not replace a regular method of contraception.

Repeated use of **ella** within the same menstrual cycle is not recommended, as safety and efficacy of repeat use within the same cycle has not been evaluated.

5.4 CYP3A4 Inducers

A CYP3A4 inducer, rifampin, decreases the plasma concentration of **ella** significantly. **Ella** should not be administered with CYP3A4 inducers [see *Drug interactions (7.1)* and *Pharmacokinetics (12.3)*].

5.5 Fertility Following Use

A rapid return of fertility is likely following treatment with **ella** for emergency contraception.

After use of **ella**, a reliable barrier method of contraception should be used with subsequent acts of intercourse that occur in that same menstrual cycle.

Because **ella** and the progestin component of hormonal contraceptives both bind to the progesterone receptor, using them together could reduce their contraceptive effect. After using **ella**, if a woman wishes to use hormonal contraception, she

should do so no sooner than 5 days after the intake of **ella**, and she should use a reliable barrier method until the next menstrual period [*see Drug Interactions (7.1 and 7.3) and Pharmacodynamics (12.2)*].

5.6 Effect on Menstrual Cycle

After **ella** intake, menses sometimes occur earlier or later than expected by a few days. In clinical trials, cycle length was increased by a mean of 2.5 days but returned to normal in the subsequent cycle. Seven percent of subjects reported menses occurring more than 7 days earlier than expected, and 19% reported a delay of more than 7 days. If there is a delay in the onset of expected menses beyond 1 week, rule out pregnancy.

Nine percent of women studied reported intermenstrual bleeding after use of **ella**.

5.7 Sexually Transmitted Infections/HIV

ella does not protect against HIV infection (AIDS) or other sexually transmitted infections (STIs).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

ella was studied in an open-label multicenter trial (Open-Label Study) and in a comparative, randomized, single-blind, multicenter trial (Single-Blind Comparative Study). In these studies, a total of 2,637 (1,533 + 1,104) women in the 30 mg ulipristal acetate groups were included in the safety analysis. The mean age of women who received ulipristal acetate was 24.5 years and the mean body mass index (BMI) was 25.3. The racial demographics of those enrolled were 67% Caucasian, 20% Black or African American, 2% Asian, and 12% other.

The most common adverse reactions ($\geq 10\%$) in the clinical trials for women receiving **ella** were headache (18% overall) and nausea (12% overall) and abdominal and upper abdominal pain (12% overall). Table 1 lists those adverse reactions that were reported in $\geq 5\%$ of subjects in the clinical studies (14).

Table 1: Adverse Reactions in $\geq 5\%$ of Women (%) Receiving a Single Dose of ella (30 mg Ulipristal Acetate)

Most Common Adverse Reactions	Open-Label Study	Single-Blind Comparative Study
	N = 1,533	N = 1,104
Headache	18	19
Nausea	12	13
Abdominal and upper abdominal pain	15	8
Dysmenorrhea	7	13
Fatigue	6	6
Dizziness	5	5

6.2 Postmarketing Experience

Adolescents: the safety profile observed in adolescents aged 17 and younger in studies and post-marketing is similar to the safety profile in adults [*see Pediatric Use (8.4)*].

The following adverse reactions have been identified during post-approval use of **ella**:

Skin and Subcutaneous Tissue Disorders: Acne

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

Several *in vivo* drug interaction studies have shown that **ella** is predominantly metabolized by CYP3A4.

7.1 Changes in Emergency Contraceptive Effectiveness Associated with Co-Administration of Other Products

Drugs or herbal products that induce CYP3A4 decrease the plasma concentrations of **ella**, and may decrease its effectiveness [*see Warnings and Precautions (5.4) and Pharmacokinetics (12.3)*]. Avoid co-administration of **ella** and drugs or herbal products such as:

- barbiturates

- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's Wort
- topiramate

Hormonal contraceptives: Progestin-containing contraceptives may impair the ability of **ella** to delay ovulation [*see Warnings and Precautions (5.5) and Pharmacodynamics (12.2)*]. Avoid co-administration of **ella** and hormonal contraceptives. If a woman wishes to start or resume hormonal contraception after the intake of **ella**, she should do so no sooner than 5 days afterwards, and she should use a reliable barrier method until the next menstrual period.

7.2 Increase in Plasma Concentrations of ella Associated with Co-Administered Drugs

CYP3A4 inhibitors such as itraconazole or ketoconazole increase plasma concentrations of **ella** [*see Pharmacokinetics (12.3)*].

7.3 Effects of ella on Co-Administered Drugs

Hormonal contraceptives: **ella** may impact the effect of the progestin component of hormonal contraceptives. Therefore, if a woman wishes to use hormonal contraception after using **ella**, she should use a reliable barrier method for subsequent acts of intercourse until her next menstrual period [*see Warnings and Precautions (5.5) and Pharmacodynamics (12.2)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X. [*See Contraindications (4).*]

Pregnancy Exposure Study

A web-based study has been established to collect information on the pregnancy outcomes of women who inadvertently receive **ella** during the cycle in which pregnancy started or at any time during pregnancy. Enroll your patient by completing the forms available at www.ellipse2.com where voluntary reports from healthcare providers or consumers are received.

Risk Summary

Use of **ella** is contraindicated during an existing or suspected pregnancy. There are no adequate and well controlled studies in pregnant women.

Data

Ulipristal acetate was administered repeatedly to pregnant rats and rabbits during the period of organogenesis. Embryofetal loss was noted in all pregnant rats and in half of the pregnant rabbits following 12 and 13 days of dosing, at daily drug exposures 1/3 and 1/2 the human exposure, respectively, based on body surface area (mg/m²). There were no malformations of the surviving fetuses in these studies. Adverse effects were not observed in the offspring of pregnant rats administered ulipristal acetate during the period of organogenesis through lactation at drug exposures 1/24 the human exposure based on AUC. Administration of ulipristal acetate to pregnant monkeys for 4 days during the first trimester caused pregnancy termination in 2/5 animals at daily drug exposures 3 times the human exposure based on body surface area.

8.3 Nursing Mothers

The breast milk of 12 lactating women following administration of **ella** was collected in 24-hour increments to measure the concentrations of ulipristal acetate and monodemethyl-ulipristal acetate in breast milk. The mean daily concentrations of ulipristal acetate in breast milk were 22.7 ng/mL [0-24 hours], 2.96 ng/mL [24-48 hours], 1.56 ng/mL [48-72 hours], 1.04 ng/mL [72-96 hours], and 0.69 ng/mL [96-120 hours]. The mean daily concentrations of monodemethyl-ulipristal acetate in breast milk were 4.49 ng/mL [0-24 hours], 0.62 ng/mL [24-48 hours], 0.28 ng/mL [48-72 hours], 0.17 ng/mL [72-96 hours], and 0.10 ng/mL [96-120 hours].

The effect of this exposure on newborns/infants has not been studied; therefore, risk to the breast-fed child cannot be excluded. Therefore, use of **ella** by breastfeeding women is not recommended.

8.4 Pediatric Use

Safety and efficacy of **ella** have been established in women of reproductive age. The clinical trials of **ella** enrolled 41 females under age 18, and a post-marketing observational study evaluating effectiveness and safety of **ella** in adolescents enrolled 279 females under age 18, including 76 under age 16 years. In these studies, the safety and efficacy profile observed in adolescents aged 17 and younger was similar to that in adults. Use of **ella** before menarche is not indicated.

8.5 Geriatric Use

This product is not intended for use in postmenopausal women.

8.6 Race

While no formal studies have evaluated the effect of race, a cross-study comparison of two pharmacokinetic studies indicated that exposure in South Asians may exceed that in Caucasians and African Americans. However, no difference in efficacy and safety was observed for women of different races in clinical studies.

8.7 Hepatic Impairment

No studies have been conducted to evaluate the effect of hepatic disease on the disposition of **ella**.

8.8 Renal Impairment

No studies have been conducted to evaluate the effect of renal disease on the disposition of **ella**.

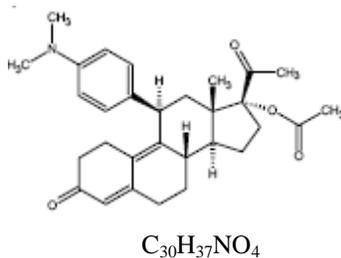
10 OVERDOSAGE

Experience with ulipristal acetate overdose is limited. In a clinical study, single doses equivalent to up to 4 times **ella** were administered to a limited number of subjects without any adverse reactions.

11 DESCRIPTION

The **ella** (ulipristal acetate) tablet for oral use contains 30 mg of a single active steroid ingredient, ulipristal acetate [17 α -acetoxy-11 β -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione], a synthetic progesterone agonist/antagonist. The inactive ingredients are lactose monohydrate, povidone K-30, croscarmellose sodium and magnesium stearate.

Ulipristal acetate is a white to yellow crystalline powder which has a molecular weight of 475.6. The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

When taken immediately before ovulation is to occur, **ella** postpones follicular rupture. The likely primary mechanism of action of ulipristal acetate for emergency contraception is therefore inhibition or delay of ovulation; however, alterations to the endometrium that may affect implantation may also contribute to efficacy.

12.2 Pharmacodynamics

Ulipristal acetate is a selective progesterone receptor modulator with antagonistic and partial agonistic effects (a progesterone agonist/antagonist) at the progesterone receptor. It binds the human progesterone receptor and prevents progesterone from occupying its receptor.

The pharmacodynamics of ulipristal acetate depends on the timing of administration in the menstrual cycle. Administration in the mid-follicular phase causes inhibition of folliculogenesis and reduction of estradiol concentration.

Pharmacodynamic data showed that administration of **ella** to 34 women in the late follicular phase postponed follicular rupture for at least 5 days in all (100%) of 8 subjects who took **ella** before the luteinizing hormone (LH) surge and 11 (79%) of 14 subjects who took **ella** immediately before ovulation (when LH has already started to rise). However, treatment was not effective in postponing follicular rupture when administered on the day of LH peak.

Dosing in the early luteal phase does not significantly delay endometrial maturation but decreases endometrial thickness by 0.6 ± 2.2 mm (mean \pm SD).

Hormonal Contraceptives after ella intake:

When a combined oral contraceptive pill (COC) containing ethinyl estradiol 30 μ g + levonorgestrel 150 μ g was started the day after **ella** intake during the follicular phase, **ella** did not interfere with the COC's ability to suppress ovarian activity, as assessed by measurement of follicle size via transvaginal ultrasound, combined with serum progesterone and estradiol levels: ovarian activity was suppressed in 61.5% (24/39) of subjects receiving **ella** plus COC and 62.2% (23/37) of subjects receiving a placebo plus the COC. The incidence of ovulation was similar between the group who received ella plus the COC [33.3% (13/39)] and the group who received a placebo plus the COC [32.4% (12/37)]. [*see Warnings and Precautions (5.5) and Drug Interactions (7.3)*].

The initiation of a desogestrel 75 μ g "progestin-only pill" the day after **ella** intake during the follicular phase was associated with a higher incidence of ovulation in the six days following **ella** intake compared to an **ella**-only treatment group, and a relatively slower onset (3 to 4 days) of thickened cervical mucus compared to a group given desogestrel without prior **ella** intake (2 days), suggesting an effect of prior use of ella on the ability of desogestrel to inhibit mucus permeability. [*See Warnings and Precautions (5.5) and Drug Interactions (7.1; 7.3)*].

12.3 Pharmacokinetics

Absorption

Following a single dose administration of **ella** in 20 women under fasting conditions, maximum plasma concentrations of ulipristal acetate and the active metabolite, monodemethyl-ulipristal acetate, were 176 and 69 ng/ml and were reached at 0.9 and 1 hour, respectively.

Figure 1: Mean (\pm SD) Plasma Concentration-time Profile of Ulipristal Acetate and Monodemethyl-ulipristal Acetate Following Single Dose Administration of 30 mg Ulipristal Acetate

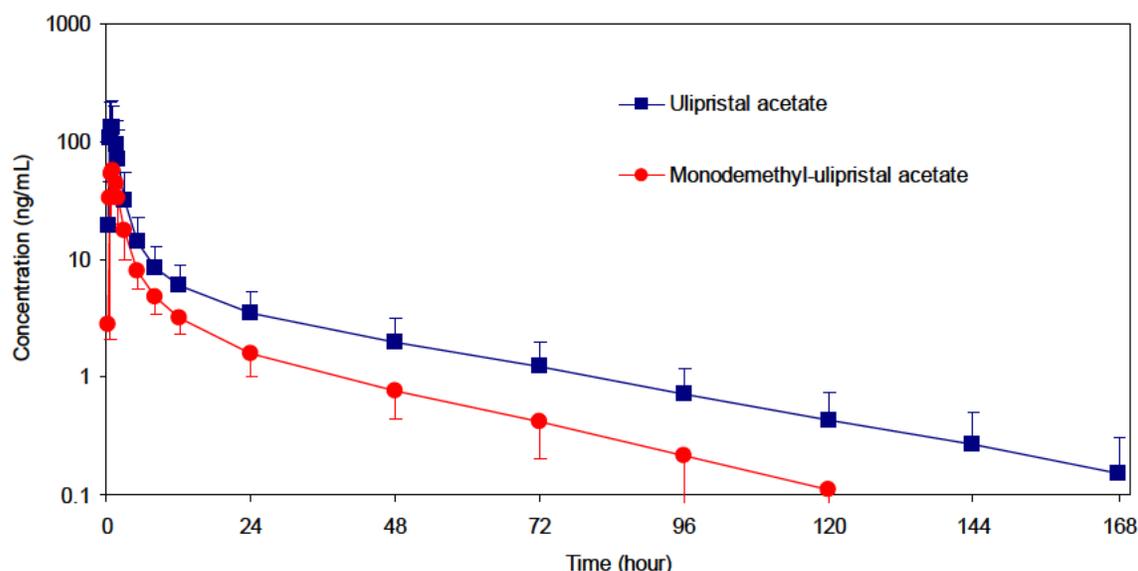


Table 2: Pharmacokinetic Parameter Values Following Administration of ella (ulipristal acetate) Tablet 30 mg to 20 Healthy Female Volunteers under Fasting Conditions

	Mean (\pm SD)				
	C_{max} (ng/ml)	AUC_{0-t} (ng·hr/ml)	$AUC_{0-\infty}$ (ng·hr/ml)	t_{max} (hr)*	$t_{1/2}$ (hr)
Ulipristal acetate	176 (89)	548 (259)	556 (260)	0.9 (0.5-2.0)	32 (6.3)
Monodemethyl-ulipristal acetate	69 (26)	240 (59)	246 (59)	1.00 (0.8-2.0)	27 (6.9)

C_{max} = maximum concentration

AUC_{0-t} = area under the drug concentration curve from time 0 to time of last determinable concentration

$AUC_{0-\infty}$ = area under the drug concentration curve from time 0 to infinity

t_{max} = time to maximum concentration

$t_{1/2}$ = elimination half-life

* Median (range)

Effect of food: Administration of **ella** together with a high-fat breakfast resulted in approximately 40 - 45% lower mean C_{max} , a delayed t_{max} (from a median of 0.75 hours to 3 hours) and 20 - 25% higher mean $AUC_{0-\infty}$ of ulipristal acetate and monodemethyl-ulipristal acetate compared with administration in the fasting state. These differences are not expected to impair the efficacy or safety of **ella** to a clinically significant extent; therefore, **ella** can be taken with or without food.

Distribution

Ulipristal acetate is highly bound (> 94%) to plasma proteins, including high density lipoprotein, alpha-l-acid glycoprotein, and albumin.

Metabolism

Ulipristal acetate is metabolized to mono-demethylated and di-demethylated metabolites. *In vitro* data indicate that this is predominantly mediated by CYP3A4. The mono-demethylated metabolite is pharmacologically active.

Excretion

The terminal half-life of ulipristal acetate in plasma following a single 30 mg dose is estimated to 32.4 ± 6.3 hours.

Drug interactions

CYP3A4 inducers: When a single 30 mg dose of ulipristal acetate was administered following administration of the strong CYP3A4 inducer, rifampin 600 mg once daily for 9 days, C_{max} and AUC of ulipristal acetate decreased by 90% and 93% respectively. The C_{max} and AUC of monodemethyl-ulipristal acetate decreased by 84% and 90% respectively [see *Drug Interactions (7.1)*].

CYP3A4 inhibitors: When a single 10 mg dose of ulipristal acetate was administered following administration of the strong CYP3A4 inhibitor, ketoconazole 400 mg once daily for 7 days, C_{max} and AUC of ulipristal acetate increased by 2- and 5.9- fold, respectively. While the AUC of monodemethyl-ulipristal acetate increased by 2.4-fold, C_{max} of monodemethyl-ulipristal acetate decreased by 47%. There was no *in vivo* drug-drug interaction study between ulipristal acetate 30 mg and CYP3A4 inhibitors [see *Drug Interactions (7.1)*].

In vitro studies demonstrated that **ella** does not induce or inhibit the activity of cytochrome P450 enzymes.

P-glycoprotein (P-gp) transporter: *In vitro* data indicate that ulipristal may be an inhibitor of P-gp at clinically relevant concentrations. When a single 60 mg dose of fexofenadine, a substrate of P-gp glycoprotein, was administered 1.5 hours after the administration of a single 10 mg dose of ulipristal acetate, there was no increase in C_{max} or AUC of fexofenadine.

Breast Cancer Resistance Protein (BCRP) transporter: *In vitro* data indicate that ulipristal acetate may be an inhibitor of BCRP at the intestinal level.

The effects of **ella** on P-gp and BCRP transporters are unlikely to have any clinical consequences when considering **ella**'s single dose treatment regimen, although there was no *in vivo* drug interaction study between ulipristal acetate 30 mg (**ella**) and substrates of P-gp and BCRP transporters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity potential was evaluated in rats and mice.

Sprague Dawley rats were exposed to ulipristal acetate daily for 99-100 weeks at doses of 1, 3, or 10 mg/kg/day, representing exposures up to 31 times higher than exposures at the maximum recommended human dose (MRHD). There were no drug-related neoplasms in male rats. In female rats, potential treatment-related neoplastic findings were limited to adrenal cortical adenomas in the intermediate dose group (3 mg/kg/day). Despite the increase, this incidence of adrenal cortical adenomas in females may not be relevant to clinical use.

Tg.rasH2 transgenic mice were exposed to ulipristal acetate for 26 weeks at doses of 5, 45, or 130 mg/kg/day, representing exposures 100 times higher than exposures at the MRHD. There was no drug-related increase in neoplasm incidence in male or female mice.

Genotoxicity: Ulipristal acetate was not genotoxic in the Ames assay, *in vitro* mammalian assays utilizing mouse lymphoma cells and human peripheral blood lymphocytes, and in an *in vivo* micronucleus assay in mice.

Impairment of Fertility: Single oral doses of ulipristal acetate prevented ovulation in 50% of rats at 2 times the human exposure based on body surface area (mg/m^2). Single doses of ulipristal acetate given on post-coital days 4 or 5 prevented pregnancy in 80-100% of rats and in 50% of rabbits when given on post-coital days 5 or 6 at drug exposures 4 and 12 times the human exposure based on body surface area. Lower doses administered for 4 days to rats and rabbits were also effective at preventing ovulation and pregnancy.

14 CLINICAL STUDIES

Two multicenter clinical studies evaluated the efficacy and safety of **ella**. An open-label study provided the primary data to support the efficacy and safety of ulipristal acetate for emergency contraception when taken 48 to 120 hours after unprotected intercourse. A single-blind comparative study provided the primary data to support the efficacy and safety of ulipristal acetate for emergency contraception when taken 0 to 72 hours after unprotected intercourse and provided supportive data for ulipristal acetate for emergency contraception when taken > 72 to 120 hours after unprotected intercourse. Women in both studies were required to have a negative pregnancy test prior to receiving emergency contraception. The primary efficacy analyses were performed on subjects less than 36 years of age who had a known pregnancy status after taking study medication.

Table 3: Summary of Clinical Trial Results for Women Who Received a Single Dose of ella (30 mg Ulipristal Acetate)

	Open-Label Study 48 to 120 Hours *	Single-Blind Comparative Study 0 to 72 Hours *
	N = 1,242	N = 844
Expected Pregnancy Rate **	5.5	5.6
Observed Pregnancy Rate ** (95% confidence interval)	2.2 (1.5, 3.2)	1.9 (1.1, 3.1)

* Time after unprotected intercourse when **ella** was taken

** Number of pregnancies per 100 women at risk for pregnancy

14.1 Open-Label Study

This study was a multicenter open-label trial conducted at 40 family planning clinics in the United States. Healthy women with a mean age of 24 years who requested emergency contraception 48 to 120 hours after unprotected intercourse received a dose of 30 mg ulipristal acetate (**ella**). The median BMI for the study subjects was 25.3 and ranged from 16.1 to 61.3 kg/m².

Twenty-seven pregnancies occurred in 1,242 women aged 18 to 35 years evaluated for efficacy. The number of pregnancies expected without emergency contraception was calculated based on the timing of intercourse with regard to each woman's menstrual cycle. **ella** statistically significantly reduced the pregnancy rate, from an expected rate of 5.5% to an observed rate of 2.2%, when taken 48 to 120 hours after unprotected intercourse.

14.2 Single-Blind Comparative Study

This study was a multicenter, single-blind, randomized comparison of the efficacy and safety of 30 mg ulipristal acetate (**ella**) to levonorgestrel (another form of emergency contraception). Subjects were enrolled at 35 sites in the U.S., the United Kingdom and Ireland, with the majority (66%) having been enrolled in the U.S. Healthy women with a mean age of 25 years who requested emergency contraception within 120 hours of unprotected intercourse were enrolled and randomly allocated to receive **ella** or levonorgestrel 1.5 mg. The median BMI for the study subjects was 25.3 and ranged from 14.9 to 70.0 kg/m².

In the **ella** group, 16 pregnancies occurred in 844 women aged 16 to 35 years when emergency contraception was taken 0 to 72 hours after unprotected intercourse. The number of pregnancies expected without emergency contraception was calculated based on the timing of intercourse with regard to each woman's menstrual cycle; **ella** statistically significantly reduced the pregnancy rate, from an expected 5.6% to an observed 1.9%, when taken within 72 hours after unprotected intercourse. There were no pregnancies observed in the women who were administered **ella** more than 72 hours after unprotected intercourse (10% of women who received **ella**).

14.3 Pooled Analysis

Data from the two studies were pooled to provide a total efficacy population of women treated with ulipristal acetate up to 120 hours after UPI. Time Trend analysis for the five 24-hour intervals from 0 to 120 hours between unprotected intercourse and treatment was conducted. There were no significant differences in the observed pregnancy rates across the five time intervals.

Subgroup analysis of the pooled data by BMI showed that for women with BMI > 30 kg/m² (16% of all subjects), the observed pregnancy rate was 3.1% (95% CI: 1.7, 5.7), which was not significantly reduced compared to the expected pregnancy rate of 4.5% in the absence of emergency contraception taken within 120 hours after unprotected intercourse. In the comparative study, a similar effect was seen for the comparator emergency contraception drug, levonorgestrel 1.5 mg. For levonorgestrel, when used by women with BMI > 30 kg/m², the observed pregnancy rate was 7.4% (95% CI: 3.9, 13.4), compared to the expected pregnancy rate of 4.4% in the absence of emergency contraception taken within 72 hours after unprotected intercourse.

16 HOW SUPPLIED/STORAGE AND HANDLING

ella (ulipristal acetate) tablet, 30 mg is supplied in a PVC-PE-PVDC-aluminum blister. The tablet is a white to off-white, round, curved tablet marked with "**ella**" on both sides.

NDC 50102-911-01 (1 tablet unit of use package)

Store at 20-25°C (68-77°F). [See USP controlled room temperature.]

Keep the blister in the outer carton in order to protect from light. **Keep out of reach of children.**

17 PATIENT COUNSELING INFORMATION

[See FDA- Approved Patient Labeling]

Information for Patients

- Instruct patients to take **ella** as soon as possible and not more than 120 hours after unprotected intercourse or a known or suspected contraceptive failure.
- Advise patients that they should not take ella if they know or suspect they are pregnant and that **ella** is not indicated for termination of an existing pregnancy.
- Advise patients to contact their healthcare provider immediately in case of vomiting within 3 hours of taking the tablet, to discuss whether to take another tablet.
- Advise patients to seek medical attention if they experience severe lower abdominal pain 3 to 5 weeks after taking **ella**, in order to be evaluated for an ectopic pregnancy.
- Advise patients to contact their healthcare provider and consider the possibility of pregnancy if their period is delayed after taking **ella** by more than 1 week beyond the date it was expected.
- A web-based study has been established to collect information on the pregnancy outcomes of women who inadvertently receive **ella** during the cycle in which pregnancy started or at any time during pregnancy. Notify patients that they can enroll by completing the forms available at www.ellipse2.com where voluntary reports from health care providers or consumers are received.
- Advise patients not to use **ella** as routine contraception, or to use it repeatedly in the same menstrual cycle.
- Advise patients that using ella and hormonal contraceptives together can affect the effectiveness of each. Advise patients to use a reliable barrier method for all subsequent acts of intercourse until the next menstrual period. If a woman wishes to use hormonal contraception, she should do so no sooner than 5 days after intake of **ella**, and she should use a reliable barrier method until the next menstrual period.
- Advise patients not to use **ella** if they are taking a CYP3A4 inducer.
- Inform patients that **ella** does not protect against HIV infection (AIDS) and other sexually transmitted diseases/infections.
- Advise patients that they should not use **ella** if they are breastfeeding because **ella** enters the breast milk.

FDA-Approved Patient Labeling
Patient Information
ella (“el-uh”)
(ulipristal acetate) tablet

Read this Patient Information Leaflet before you take **ella**. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is ella?

ella is a prescription emergency contraceptive that reduces your chance of becoming pregnant if your birth control fails or you have unprotected sex.

ella should not be used as your regular birth control. It is very important that you have a reliable form of birth control that is right for you.

ella will not protect you against HIV infection (AIDS) and other sexually transmitted diseases (STDs).

Who should not take ella?

- Do not take **ella** if you know or suspect you are already pregnant. **ella** is not for use to end an existing pregnancy. Talk to your healthcare provider before taking **ella** if you think you are pregnant.
- Do not take **ella** if you are breastfeeding because **ella** gets into the breast milk.

What should I tell my healthcare provider before taking ella?

See “Who should not take **ella**?”

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Using some other medicines may make **ella** less effective. These include St. John’s Wort, phenytoin, rifampin, phenobarbital and carbamazepine. Talk to your healthcare provider about whether **ella** is right for you if you are currently using these medications. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

What should I do about birth control after I take ella?

Using **ella** with hormonal contraceptives such as birth control pills could reduce the effectiveness of both drugs to prevent pregnancy. After using **ella**, if you wish to use hormonal contraception, you should do so no sooner than 5 days after the intake of ella. Be sure to use a reliable barrier contraceptive method (such as a condom with spermicide) each time you have sex until your hormonal birth control has taken effect.

If you do not use hormonal contraception, after using **ella**, you should use a reliable barrier contraceptive method (such as condom with spermicide) each time you have sex.

When is it not appropriate to use ella?

- Do not use **ella** as a regular birth control method. It does not work as well as most other forms of birth control when they are used consistently and correctly.
- Do not use **ella** if you are already pregnant.
- Do not use **ella** more than one time in the same menstrual cycle for different acts of unprotected sex or birth control failure.

How does ella work?

ella is thought to work for emergency contraception primarily by stopping or delaying the release of an egg from the ovary. It is possible that **ella** may also work by preventing attachment (implantation) to the uterus.

How should I take ella?

- Take **ella** as soon as possible within 5 days (120 hours) after unprotected sex or if you had a birth control failure.
- **ella** can be taken with or without food.
- Contact your healthcare provider right away if you vomit within 3 hours of taking **ella**. Your healthcare provider may prescribe another dose of **ella** for you.
- **ella** can be taken at any time during the menstrual cycle.

How effective is ella?

If **ella** is taken as directed, it will reduce the chance that you will get pregnant. **ella** is not effective in every case. **ella** is only to be used for a single episode of unprotected intercourse. Be sure to use a regular birth control method the next time you have sex.

ella and other emergency contraceptives may be less effective in women with a body mass index (BMI) > 30 kg/m².

What if I am already pregnant and use ella?

ella should not be taken if you are already pregnant. There is little information on whether **ella** would harm a developing baby. Contact your healthcare provider if you think you may be pregnant and have taken **ella**.

If you are pregnant and have taken **ella**, you are encouraged to provide information on your pregnancy on a dedicated website. The purpose of this website is to collect information about the safety of **ella** in women who have taken it during pregnancy. For information about how to sign up for this website, go to www.ellipse2.com.

ella is not for use to terminate an existing pregnancy.

What should I do if my menstrual period is delayed beyond 1 week or I have severe lower stomach (abdominal) pain?

After taking **ella**, your next menstrual period may begin a few days earlier or later than expected. If your period is more than 7 days later than expected, you may be pregnant. You should get a pregnancy test and follow up with your healthcare provider.

If you are pregnant and have taken **ella**, you are encouraged to provide information on your pregnancy on a dedicated website. See "What if I am already pregnant and use ella?"

If you have severe lower stomach (abdominal) pain about 3 to 5 weeks after taking **ella**, you may have a pregnancy outside of the uterus (womb), which is called an ectopic or tubal pregnancy. An ectopic pregnancy is a serious condition that needs medical treatment right away. Call your healthcare provider or go to the nearest emergency room right away if you think you may have an ectopic pregnancy.

How often can I use ella?

ella is meant for emergency contraception only, and is not to be used frequently or as a regular birth control. If you need to use emergency contraception often, talk to your healthcare provider and learn about methods for birth control and sexually transmitted disease prevention that are right for you.

What are the possible side effects of ella?

The most common side effects of **ella** include:

- headache
- nausea
- stomach (abdominal) pain
- menstrual pain (dysmenorrhea)
- tiredness

- o dizziness

Some women taking **ella** may have their next period earlier or later than expected. If your period is more than a week late, you should get a pregnancy test.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **ella**. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA 1-800-FDA-1088.

How should I store ella?

- o Store **ella** at 68-77°F (20-25°C).
- o Protect **ella** from light. Keep **ella** in the blister card inside the original box until you are ready to take it.

Do not use **ella** if the package is torn or broken.

Keep **ella** and all medicines out of the reach of children.

General information about the safe and effective use of ella:

Medicines are sometimes prescribed for purposes other than those in a Patient Information Leaflet. Do not use **ella** for a condition for which it was not prescribed. Do not give **ella** to other people, even if they have the same symptoms that you have. It may harm them.

In the case of an overdose, get medical help or contact a Poison Control Center right away at 1-800-222-1222. Overdose experience with **ella** is limited.

This Patient Information Leaflet summarizes the most important information about **ella**. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about **ella** that is written for health professionals.

For more information, go to www.ella-rx.com or you can contact Afaxys, Inc. Health and Safety Team at 1-855-888-2467.

What are the ingredients in ella?

Active ingredients: ulipristal acetate, 30 mg

Inactive ingredients: lactose monohydrate, povidone, croscarmellose sodium, and magnesium stearate

For all medical inquiries contact:

Afaxys, Inc.
Health and Safety Team
Charleston, SC, 29403, USA
1-855-888-2467

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Charleston, SC, 29403, USA

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/s/

AUDREY L GASSMAN
03/10/2015