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)

DOSE 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)

DOSE FORMS AND STRENGTHS
• 30 mg tablet (3)
• 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 (≥ 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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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 (5.5) and Pharmacokinetics (12.3)]. Avoid co-administration of ella and drugs or herbal products such as:

- barbiturates
- bosentan
- carafenamate
- felbamate
- griseofulvin
- oscarbazepine
- 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 iraconazole 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 act 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. Ulipristal acetate was administered to a limited number of subjects without any adverse reactions.

8.2 Nursing Mothers

ella is contraindicated during breast feeding. There are no adequate and well controlled studies in nursing women.

ella was administered to pregnant monkeys for 4 days during the first trimester caused pregnancy termination in 2/5 animals through lactation at drug exposures 1/24 the human exposure based on AUC. Administration of ulipristal acetate to pregnant rats and rabbits during the period of organogenesis did not alter development. The pharmacokinetics of ulipristal acetate depend 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 ± SD).

Hormonal Contraceptives after ella intake:

When a combined oral contraceptive pill (COC) containing ethinyl estradiol 30 µg + levonorgestrel 150 µg 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 (7.5)].

The use of a desogestrel 75 µg “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 49 ng/mL and were reached at 0.9 and 1 hour, respectively.

Table 1: Monodemethyl-ulipristal Acetate Plasma Concentration-time Profile of Ulipristal Acetate and Monodemethyl-ulipristal Acetate Following Single Dose Administration of 30 mg Ulipristal Acetate

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24</td>
<td>Ulipristal acetate</td>
</tr>
<tr>
<td></td>
<td>Monodemethyl-ulipristal acetate</td>
</tr>
<tr>
<td>0-24</td>
<td>176 (89)</td>
</tr>
<tr>
<td></td>
<td>69 (26)</td>
</tr>
<tr>
<td>0-120</td>
<td>548 (259)</td>
</tr>
<tr>
<td></td>
<td>240 (59)</td>
</tr>
<tr>
<td>0-180</td>
<td>556 (260)</td>
</tr>
<tr>
<td></td>
<td>246 (59)</td>
</tr>
<tr>
<td>0-240</td>
<td>246 (260)</td>
</tr>
<tr>
<td></td>
<td>140 (59)</td>
</tr>
<tr>
<td>0-360</td>
<td>140 (259)</td>
</tr>
<tr>
<td></td>
<td>90 (59)</td>
</tr>
</tbody>
</table>

Table 2: Pharmacokinetic Parameter Values Following Administration of ella (ulipristal acetate)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum concentration (Cmax)</td>
<td>176 (89) ng/mL</td>
</tr>
<tr>
<td>Area under the drug concentration curve from time 0 to time of last determinable concentration (AUC0-t)</td>
<td>556 (260) ng*h/mL</td>
</tr>
<tr>
<td>Time to maximum concentration (tmax)</td>
<td>0.9 (0.5-2.0)小时</td>
</tr>
<tr>
<td>Elimination half-life (t1/2)</td>
<td>32 (6.3)小时</td>
</tr>
</tbody>
</table>

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

CH3
H
O
N
C

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

Effect of food: Administration of ella together with a high-fat breakfast resulted in approximately 40-45% lower exposure (Cmax and AUC0-t) compared to administration on an empty stomach. However, 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.

ella
Ulipristal acetate

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 UI. 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. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING
ella (ulipristal acetate) tablet, 30 mg is supplied in a PVC-P-E-PVD-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°C-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.ellipere2.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.

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

<table>
<thead>
<tr>
<th></th>
<th>Open-Label Study 48 to 120 Hours</th>
<th>Single-Blind Comparative Study 0 to 72 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1,242</td>
<td>N = 844</td>
</tr>
<tr>
<td>Expected Pregnancy Rate **</td>
<td>5.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Observed Pregnancy Rate **</td>
<td>2.2 (1.5, 3.2)</td>
<td>1.9 (1.1, 3.1)</td>
</tr>
</tbody>
</table>

** 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).
FDA-Approved Patient Labeling
Patient Information
ella ("ell-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.
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 medicines. 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 works if you are already pregnant. Other emergency contraceptives may be less effective in women with a BMI > 30 kg/m².

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.ella-rx.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 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
• 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 1800-FDA-1088.

How should I store ella?
Store ella at 68-77°F (20-25°C).
• 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 1-800-2221222.

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.

For information about ella that is written for health professionals, go to www.ella-rx.com or you can contact Afaxys, Inc. Health and Safety Team at 1855-888-2467.

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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