

PRODUCT MONOGRAPH

Pr ella®

Ulipristal Acetate Tablet

Tablet, 30 mg

Emergency Contraceptive

<p>Laboratoire HRA Pharma 200 avenue de Paris, 92320 Chatillon, France www.hra-pharma.com</p> <p>Imported and distributed by: Allergan Inc. Markham, Ontario L6G 0B5 CANADA</p>	<p>Date of Preparation: May 12, 2016</p> <p>Date of Revision: June 19, 2019</p>
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Pr ella®

Ulipristal Acetate Tablet

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY OF PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet, 30 mg	Lactose Monohydrate <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

ella® (ulipristal acetate) is indicated for:
prevention of pregnancy when taken within 120 hours (5 days) of unprotected intercourse or a known or suspected contraceptive failure. Ella is not intended for routine use as a contraceptive.

CONTRAINDICATIONS

- ella® is contraindicated in women who are hypersensitive to ulipristal acetate or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- ella® is contraindicated in women with known or suspected pregnancy. If there is a doubt regarding pregnancy following a previous act of intercourse, especially if there is recent abnormal bleeding, a pregnancy test should be performed before taking ella® (See [Specific Populations](#)).

WARNINGS AND PRECAUTIONS

General

Emergency Contraceptives **DO NOT PROTECT** against Sexually Transmitted Infections (STIs) including HIV/AIDS.

Emergency contraception does not prevent pregnancy in every case.

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**[®].

ella[®] is not intended for routine use as a contraceptive. It has been approved for emergency contraception only. In phase III clinical trials, repeated use in different cycle was allowed however few data are available up to three administrations over a time period of 1 to 12 months. If a woman is a repeat user of an emergency contraception, other contraceptive options should be discussed with her.

The efficacy of **ella**[®] in women with a body mass index (BMI) of ≥ 35 kg/m² has not been evaluated.

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

Hepatic/biliary/pancreatic

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

No alternate dose recommendations for **ella**[®] can be made.

Severe hepatic impairment: **ella**[®] is not recommended.

Renal

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

No alternate dose recommendations for **ella**[®] can be made.

CYP3A4 Inducers

A CYP3A4 inducer, rifampin, decreases the plasma concentration of **ella**[®] significantly. **ella**[®] should not be administered with CYP3A4 inducers (see DRUG INTERACTIONS and Pharmacokinetics).

Potential for ulipristal acetate to affect other hormonal contraceptives:

Because ulipristal acetate binds to the progesterone receptor with high affinity, it may interfere with the action of progestogen-containing medicinal products. Contraceptive action of combined hormonal contraceptives and progestogen-only contraception may be reduced (see DRUG INTERACTIONS).

Sexual Function/Reproduction

Existing pregnancy: **ella**[®] is not indicated for termination of an existing pregnancy. If there is a doubt regarding pregnancy following a previous act of intercourse, especially if there is recent abnormal bleeding, a pregnancy test should be performed before 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**[®].

Ectopic pregnancy: if pregnancy occurs after treatment, the possibility of an ectopic pregnancy should be considered. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding. 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**[®].

Effects on menstrual cycle: after taking **ella**[®], menses sometimes occurs a few days earlier or later than expected. If there is a delay in the onset of expected menses beyond 1 week, pregnancy testing should be undertaken.

Fertility following use: a rapid return of fertility is likely following treatment with **ella**[®]; therefore, routine contraception should be continued or initiated as soon as possible following use of **ella**[®] to ensure ongoing prevention of pregnancy. While there are no data about use of **ella**[®] with regular hormonal contraceptives, due to its high affinity binding to the progesterone receptor, use of **ella**[®] may reduce the contraceptive action of regular hormonal contraceptive methods. 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.

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.

Special Populations

Pregnant Women:

Use of **ella**[®] is contraindicated in women with known or suspected pregnancy. **ella**[®] does not interrupt a pregnancy. Pregnancy may occasionally be detected after **ella**[®] intake.

Limited human data regarding pregnancy exposure to **ella**[®] do not suggest any safety concern.

Although no teratogenic potential has been observed, animal data are insufficient with regard to reproduction toxicity. (see TOXICOLOGY)

Nursing Women: ulipristal acetate is present in breast milk after taking **ella**[®]. The effect on newborn/infants has not been studied. A risk to the breast-fed child cannot be excluded.

Therefore, use of **ella**[®] by breastfeeding women is not recommended.

Pediatrics: Safety and efficacy of **ella**[®] have been established in women of reproductive age. However, Safety and efficacy data of **ella**[®] are limited in women between 16 years of age and 18 years of age. Safety and efficacy are expected to be the same for postpubertal adolescents less than 18 years and for users 18 years and older. Use of **ella**[®] before menarche is not indicated.

Geriatrics: **ella**[®] has not been studied in this population and is not intended for use in postmenopausal women.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The common adverse reactions ($\geq 5\%$) in the clinical trials for women receiving **ella**[®] were headache (9%), nausea (9%), abdominal pain (5%) dysmenorrhea (5%), fatigue and dizziness.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for estimating rates.

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.

Adverse events observed in at least 1% of patients treated with **ella**[®] are shown in Table 1.

Table 1 Treatment-Related Adverse Events Occurring in $\geq 1\%$ of Patients in Clinical Trials

Most Common Adverse Reactions (MedDRA)	Open-Label Study	Single-Blind Comparative Study		Pooled Results
	Ulipristal acetate 30 mg N = 1,533 (%)	Ulipristal acetate 30 mg N = 1,104 (%)	Levonorgestrel 1.5 mg N = 1,117 (%)	Ulipristal acetate 30 mg N = 2,637 (%)
Nausea	9.2	9.4	8.1	9.3
Headache	9.3	8.4	7.5	9.0
Dysmenorrhea	4.1	7.0	8.4	5.3
Abdominal pain (unspecified)	6.8	3.1	4.5	5.2
Fatigue	3.4	3.6	2.6	3.5
Dizziness	3.5	3.1	3.0	3.3
Upper abdominal pain	2.2	1.8	2.9	2.0
Pelvic pain	2.2	0.1	0.2	1.3
Back pain	1.0	1.3	0.6	1.1
Vomiting	1.0	1.0	0.4	1.0

In the single-blind comparative study, a similar adverse events profile was observed between the ulipristal acetate and levonorgestrel groups.

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

Clinical laboratory testing was performed in 112 subjects, who had both screening and end-of-study clinical laboratory assessments during phase 3 trials. One subject with a normal hepatic

panel at screening presented an isolated and moderate increase in ALT and in AST (ALT=74, normal limits <55 units/L); (AST=88, normal limits<45 units/L) 12 days after ulipristal acetate intake. No other laboratory abnormality was considered as related to the drug by the investigator. No abnormal liver function results were observed in women exposed to multiple doses of ulipristal acetate in the phase 3 program.

Three subjects with normal values at screening had haemoglobin values slightly below the lower limit of normal at the end of the study.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Metabolism and nutrition disorder: appetite disorders

Psychiatric disorders: emotional disorder, anxiety, sleep disorders, hyperactivity disorder, libido changes

Nervous system disorders: tremor, dysgeusia, syncope

Eye disorders: visual disturbances, abnormal sensation in eye, ocular hyperaemia, photophobia

Ear and labyrinth disorders: vertigo

Gastrointestinal disorders: diarrhea, dry mouth, dyspepsia

Skin and subcutaneous tissue disorders: acne, allergic skin reactions

Reproductive system and breast disorders: menorrhagia, vaginal discharge, vaginitis, menstrual disorders, metrorrhagia, hot flush, premenstrual syndrome, genital pruritus, dyspareunia, ruptured ovarian cyst, vulvovaginal pain

General disorders and administration site conditions: malaise

Post –market adverse drug reactions

The adverse reactions spontaneously reported in post-marketing were similar in nature and frequency to the safety profile described during the phase III program.

The following adverse reactions have been identified during post-approval use of **ella**[®]: Skin and Subcutaneous Tissue Disorders: Acne

DRUG INTERACTIONS

Drug-Drug Interactions

Potential for other medicinal products to affect ulipristal acetate:

Ulipristal acetate is metabolized *in vitro* by CYP3A4.

- CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St John's wort/*Hypericum perforatum*, barbiturates, bosentan, carbamazepine, felbamate, griseofulvin, oxcarbazepine, topiramate) may reduce plasma concentrations of ulipristal acetate and may result in decreased efficacy. Concomitant use is therefore not recommended.
- The CYP3A4 inhibitor ritonavir can also have an inducing effect on CYP3A4 when ritonavir is used for a longer period. In such cases ritonavir might reduce plasma concentrations of ulipristal acetate. Concomitant use is therefore not recommended. Enzyme induction wears

off slowly and effects on the plasma concentrations of ulipristal acetate may occur even if a woman has stopped taking an enzyme inducer within the last 2-3 weeks

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

Potential for ulipristal acetate to affect other medicinal products:

Because ulipristal acetate binds to the progesterone receptor with high affinity, it may interfere with the action of progestogen-containing medicinal products:

- Contraceptive action of combined hormonal contraceptives and progestogen-only contraception may be reduced
- Concomitant use of ulipristal acetate and emergency contraception containing levonorgestrel is not recommended.

In vitro studies demonstrated that **ella**[®] does not induce or inhibit the activity of cytochrome P450 enzymes. Thus, administration of ulipristal acetate is unlikely to alter the clearance of medicinal products that are metabolised by these enzymes.

P-glycoprotein (P-gp) transporters: *In vitro* data indicate that ulipristal may be an inhibitor of P-gp at clinically relevant concentrations. Thus, co-administration of ulipristal acetate and P-gp substrates (e.g., dabigatran etexilate, digoxin) may increase the concentration of P-gp substrates. *In vivo* data suggest that ulipristal acetate 10 mg does not affect P-gp transporters. However, there was no *in vivo* drug interaction study between ulipristal acetate 30 mg and P-gp transporters (see Pharmacokinetics).

Drug-Food Interactions

The tablet can be taken with or without food (See section “Pharmacokinetics”).

Drug-Herb Interactions

Interactions with herbal products have not been established. Nevertheless St. John’s wort as a CYP3A4 inducer decreases the plasma concentrations of ulipristal acetate, and may decrease its effectiveness (See section “Drug-Drug Interactions”).

Drug-Laboratory Test Interactions

No laboratory test interactions were observed during clinical evaluations.

DOSAGE AND ADMINISTRATION

Instruct patient to take one tablet orally as soon as possible within 5 days (120 hours) 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, another tablet should be taken.

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

OVERDOSAGE

Experience with ulipristal acetate overdose is limited. Single dose up to 200 mg were administered to a limited number of subjects, and no severe or serious adverse reactions were reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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.

Pharmacodynamics

Ulipristal acetate is a selective progesterone receptor modulator with antagonistic and partial agonistic effects at the progesterone receptor. It binds to 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 , reduction of estradiol concentration and a delay in menstrual bleeding by 2 days on average. Administration at the time of the luteinizing hormone peak delays follicular rupture by 5 to 10 days. Dosing in the early luteal phase does not significantly delay endometrial maturation but slightly decreases endometrial thickness. Dosing in mid-luteal phase induces early bleeding and longer menstrual bleeding period at the highest dose (200 mg).

Pharmacokinetics

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-∞} (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-∞} = 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)

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.

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-∞} 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.

Ulipristal acetate is a lipophilic compound and is distributed in breast milk, with a mean daily excretion of 13.35 µg [0-24 hours], 2.16 µg [24-48 hours], 1.06 µg [48-72 hours], 0.58 µg [72-96 hours], and 0.31 µg [96-120 hours].

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).

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).

P-glycoprotein (P-gp) transporters: 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.

STORAGE AND STABILITY

Store at 15-25°C. Store in the original packaging to protect from moisture. Keep the blister in the outer carton to protect from light.

Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ella[®] (ulipristal acetate) tablet, 30 mg is supplied in a PVC-PE-PVDC-aluminum blister. The tablet is a white to marble creamy, round, curved tablet marked with “ella” on both sides.

The inactive ingredients are croscarmellose sodium, lactose monohydrate, magnesium stearate and povidone K-30.

(1 tablet unit of use package)

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

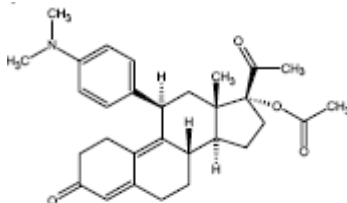
Drug Substance

Proper Name: ulipristal acetate

Chemical name: 19-Norpregna-4,9-diene-3,20-dione, 17-(acetyloxy)-11-[4-(dimethylamino)phenyl]-, (11 β)-

Molecular formula and molecular mass: C₃₀H₃₇NO₄; 475.6

Structural formula:



Physiochemical properties: Ulipristal acetate is a white to yellow crystalline powder

CLINICAL TRIALS

Two pivotal 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 120 hours after unprotected intercourse and supported the indication of ulipristal acetate for emergency contraception when taken up 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 who had known pregnancy status after taking study medication.

1/ Study Demographic and Trial Design

Open label study (study HRA2914-509)

This study was a multicenter open-label trial conducted in the United States. Healthy women (n=1241) 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**[®]).

Single-blind comparative study (study HRA2914-513)

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 44 sites in three countries, with the majority (66%) having been enrolled in the United States. Healthy women (n= 1893) with a mean age of 25 years who requested emergency contraception within 120 hours of unprotected intercourse were involved and randomly allocated to receive **ella**[®] or levonorgestrel 1.5 mg. Table 3 summarizes the main elements of trial design and Table 4 the baseline demographic characteristics for the 2 pivotal phase 3 efficacy and safety trials.

Table 3 Overview of design of phase 3 efficacy studies

	Open label study	Single blind comparative study
Design	Open label (study 509)	Randomized single blind comparative (study 513)
Time window	48 – 120 h after intercourse	Within 120 h of intercourse
Study sites	45 family planning clinics (USA)	35 family planning clinics (24 USA, 10 UK, 1 Ireland)
Treatments	Ulipristal acetate 30 mg	Ulipristal acetate 30 mg Levonorgestrel 1.5 mg
Study schedule	FU visit 5-7 days after expected onset of menses to verify pregnancy status by urine pregnancy testing and return of menses. Additional visit 1 week later as needed to ascertain pregnancy status	
Primary efficacy analysis	Comparison of the observed pregnancy rate to the expected pregnancy rate in the mITT population	
		Non-inferiority UPA to LNG
Condition of study success	Positive outcome for primary efficacy analysis AND inferiority to clinical interest limit of 4%	
Safety reporting	Adverse events, vaginal bleeding and lab parameters (subset of patients)	Adverse events & vaginal bleeding

Table 4 Overview of demographics of pivotal efficacy studies

	Open label study	Single blind comparative study	
	Ulipristal acetate 30mg 48-120 h N=1,533	Ulipristal acetate 30mg 0-120 h N = 1,104	Levonorgestrel 1.5mg 0-120 h* N = 1,117
Age (years)			
- Mean ± SD	24.4 ± 6.1	24.5 ± 6.1	24.9 ± 6.5
- Range	18-50	16-52	16-55
- 16 – 20	446 (29.1%)	347 (31.4%)	328 (29.4%)
- 21 – 25	611 (39.9%)	362 (32.8%)	364 (32.6%)
- 26 – 30	258 (16.8%)	215 (19.5%)	229 (20.5%)
- 31 – 35	119 (7.8%)	108 (9.8%)	113 (10.1%)
- ≥ 36	99 (6.5%)	72 (6.5%)	83 (7.4%)
Race, n (%)			
- White	921 (60.3%)	804 (72.8%)	809 (72.4%)
- Black or African American	328 (21.5%)	210 (19.0%)	207 (18.5%)
- Other (including Asian, Hawaiian and Other Pacific Islander)	279 (18.3%)	90 (8.2%)	101 (9.1%)
Body mass index (kg/m²)			
- Mean ± SD	25.3 ± 6.2	25.3 ± 5.9	25.2 ± 5.7
Average menstrual cycle length, days (range)	29.0 (24 – 35)	28.7 (24 – 35)	28.8 (23 – 40)
% women with regular periods in the previous year	96.0%	98.6%	98.7%
Average bleeding days	4.7	4.7	4.7
(% of women with)	3.3%	0.8%	1.3%
- intermenstrual bleeding	7.1%	2.5%	2.7%
- amenorrhea or oligomenorrhea			
% women with previous pregnancy	52.4%	47.3%	47.8%
% couples using male condoms within 3 months prior to inclusion	71.7%	82.1%	83.7%
% women having used EC in the past	52.5%	54.9%	55.7%
Number of acts of unprotected intercourse prior to enrollment within the treatment cycle			
(% of women with)			
- 0 intercourse	0.6%	0.1%	0.3%
- 1 intercourse	84.9%	89.4%	88.5%
- 2 intercourses	11.2%	7.5%	9.0%
- 3 intercourses	2.3%	2.1%	1.9%
- 4 intercourses	0.8%	0.9%	0.4%
- 5 or more intercourses	0.2%	0.0%	0.0%
Time elapsed between intercourse and treatment			
(% of women enrolled in)			
- ≤ 24 h	-	33.0%	35.0%
- 25-48 h	-	35.0%	34.0%
- 48-72 h	69.2%	22.0%	20.0%

- 73-96 h	32.9%	7.0%	8.0%
- ≥ 97 h	13.1%	3.0%	3.0%

* Levonorgestrel 1.5 mg is approved to be used only up to 72 hours after intercourse.

2/ Summary of clinical trial results for ella®

Main results from the two phase 3 pivotal trials are summarized in Tables 5 and 6.

Table 5 Comparison of observed vs. expected pregnancy rates

	Open label study mITT population (primary efficacy variable) 0-120 h		Single blind comparative study mITT population 0-72 h	
	Ulipristal acetate (n = 1241)	Ulipristal acetate (n=843)	Levonorgestrel (n=851)	
Observed pregnancies (n)	26	15	22	
Expected pregnancy rate (%)	5.53%	5.54%	5.43%	
Observed pregnancy rate (%; 95% CI)	2.10 (1.41 - 3.10)	1.78 (1.04 – 2.98)	2.59 (1.68 – 3.94)	
Comments:	UL95% CI = 3.10 < 4% < 5.53% Efficacy significantly better than the unacceptable rate (5.53%) and clinical interest limit (4%)	UL95% CI = 2.98 < 4% < 5.54% Better than the unacceptable rate (5.54%) and clinical interest limit (4%)	UL95% CI = 3.94 < 4% < 5.43% Better than the unacceptable rate (5.43%) and close to clinical interest limit (4%)	

Table 6 Pregnancy rates by time from unprotected intercourse to ella® treatment

Time from intercourse to treatment (h)	< 24		24-48		48-72		73-96		97-120	
	SBCS ¹	OLS ²	SBCS	OLS	SBCS	OLS	SBCS	OLS	SBCS	OLS
N of subjects included	312		329		203	693	63	390	34	158
N of observed pregnancies	5		7		3	16	0	8	0	2
Pregnancy rate (%)	1.6		2.13		1.48	2.30	0.00	2.04	0.00	1.26
Odds ratio ³ (95% CI)	NA		1.33 (0.42-4.25)		0.69 (0.18-2.70)	NA	0.00	0.89 (0.38-2.09)	NA	0.61 (0.13-2.92)

¹ Single blind comparative study

² Open label study

³ Odds ratio at a given time interval is relative to the previous 24-h time interval.

The results of the two trials were consistent and statistically conclusive: ella® significantly decreased the risk of pregnancy after unprotected intercourse, from an estimated expected pregnancy rate of 5.5% to observed pregnancy rates of 2.1% (95% CI [1.41-3.10]) in the open-label study and 1.78% (95% CI [1.04-2.98%]) in the comparative study. The observed pregnancy rate in the levonorgestrel comparator group was 2.59% (95% CI [1.68-3.94]).

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.

DETAILED PHARMACOLOGY

i. Pharmacodynamics

The pharmacological profile of ulipristal acetate has been investigated in a variety of studies, both *in vitro* and *in vivo*. These studies have shown it to be a modulator of the progesterone receptor with lesser antagonistic activity at the glucocorticoid receptor. Safety pharmacology studies have not shown any other activities of concern, even at concentrations and doses considerably higher than those required for progesterone receptor antagonism.

1. Human

a. HRA2914-511 and HRA2914-576

In this study, 35 women were administered placebo or 30 mg ulipristal acetate in alternate cycles in a cross-over design when the leading follicle reached 18mm, at the presumed time of the LH surge.

In placebo cycles, all dominant follicles had ruptured by 5 days after treatment. In contrast, the dominant follicle persisted for at least 5 days in 20/34 (58.8%) ulipristal acetate cycles. The difference between ulipristal acetate and placebo was highly significant ($p < 0.0001$). The magnitude of inhibition of follicular rupture differed according to LH status at the time of treatment. When ulipristal acetate was administered before LH surge onset, dominant follicle was still present in 100% (8/8) of cycles at 5 days. When given after the LH surge but prior to the peak, follicular rupture inhibition in the five day period was 78.6% (11/14). In contrast, when ulipristal acetate was given after LH peak level was reached, follicle rupture inhibition was observed only in 1/12 (8.3%) of ulipristal acetate cycles (Table 7).

Table 7 Inhibition of follicular rupture at 5 days after treatment administration, stratified by LH status at time of treatment

	Ulipristal acetate n (%) [95% CI]	Placebo n (%) [95% CI]
Treatment before LH surge onset	8/8 (100%) [-]	0/12 (0%) [-]
Treatment after LH surge onset but before LH peak	11/14 (78.6%) [49.2-95.3]	0/6 (0%) [-]
Treatment after LH peak	1/12 (8.3%) [0.2-38.5]	0/16 (0%) [-]

CI: confidence interval

Menstrual cycle length (adjusted for baseline cycle duration) was significantly increased after ulipristal acetate treatment compared to placebo (32.7 ± 3.7 and 30.2 ± 4.1 days, respectively, $p=0.0024$).

The raw data from this study were pooled with two other similar studies conducted by the same investigators comparing various EC regimens, and showed that ulipristal acetate was significantly more effective than levonorgestrel in inhibiting ovulation once the lead follicle had reached 18 mm, a critical time in the cycle when the risk of pregnancy peaks (Brache *et al.* 2013, online publication in *Contraception*-HRA2914-576). The results of this analysis suggest that ulipristal acetate is able to delay follicular rupture for at least 5 days in a significantly higher proportion of women than levonorgestrel when given in the late follicular phase, at the time when the LH peak and ovulation are imminent (see Table 8).

Table 8 Proportion of unruptured dominant follicles 5 days after EC intake in the late follicular phase

	Placebo n=50	Levonorgestrel n=48	Ulipristal acetate n=34
Treatment before LH surge	0.0%	25.0%	100% $P<0.005^*$
Treatment after LH surge but before LH peak	10.0%	14.3% NS†	78.6% $P<0.005^*$
Treatment after LH peak	4.2%	9.1% NS†	8.3% NS*

*: compared to levonorgestrel and to placebo. NS: non statistically significant. †: compared to placebo

b. HRA2914-505 mid-follicular single dose administration

In this study, 45 women were given either placebo or ulipristal acetate in a single dose (10, 50 or 100 mg) during the mid-follicular phase when they had a dominant ovarian follicle that was approximately 16 mm.

The treatment effect on the menstrual cycle length was dose-dependent. The 50 and 100mg dose groups had treatment cycles that were on average 4 days longer than the placebo and 10 mg groups ($p < 0.01$). The treatment cycle was lengthened by 1-2 weeks in 30% at 100mg, 27% at 50mg and 9% at 10mg. This increase was due to a 1 week delay in menses observed in only 8 subjects (1 at 10mg, 3 at 50mg, and 4 at 100mg).

2. Animal

Administration of ulipristal acetate to rats on the day of proestrus inhibited ovulation at oral doses of 0.5 mg/rat and above. When administered as single 2 mg oral doses, ulipristal acetate was without effect in preventing pregnancy when given on days 0, 1, 2 or 3 post mating but was highly effective when administered on day 4 with slightly less effect on day 5. The post-coital effect could be blocked by coadministration of progesterone. In rabbits, greater activity of single doses was observed on days 5 or 6 post mating than on day 4.

3. In vitro

Table 9 Binding of ulipristal acetate and its active metabolite CDB 3877 to the progesterone and glucocorticoid receptors

Compound	rhPR-B		rhPR-A		Rabbit PR		Rabbit GR	
	EC ₅₀	RBA	EC ₅₀	RBA	EC ₅₀	RBA	RC ₅₀	RBA
Ulipristal acetate	7.7±0.5	99	8.5±10.6	101	13.6±0.6	85	15.4±1.3	53
Monodemethylated ulipristal acetate	8.8±0.2	78	11.6±1.0	74	11.8±0.9	101	14.7±0.8	55

EC₅₀ values in nM; RBA in % relative to values of 100% for progesterone or dexamethasone

ii. Pharmacokinetics

1. Human

a. Absorption: HRA2914-512 (table 10)

Individual absorption parameters in fasted and fed states for both ulipristal acetate and its main monodimethylated metabolite are summarized in the table below.

Table 10 Summary of ulipristal acetate and 3877A pharmacokinetic parameters

Parameter	Ulipristal		3877A	
	Fasted	Fed	Fasted	Fed
C _{max} (ng/mL)	173 ± 68.5	99.2 ± 44.3	86.5 ± 30.0	54.0 ± 21.9
t _{max} (h)	0.75 (0.50 – 1.50)	3.00 (0.50 – 5.00)	0.75 (0.50 – 1.50)	3.00 (0.50 – 5.00)
t _{lag} (h)	0.00 (0.00 – 0.00)	0.00 (0.00 -0.50)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.50)
AUC _{0-t} (h.µg/mL)	0.467 ± 0.243	0.566 ± 0.285 ^a	0.244 ± 0.0836	0.294 ± 0.0934 ^a
AUC _{0-∞} (h.µg/mL)	0.474 ± 0.256 ^a	0.608 ± 0.292 ^b	0.265 ± 0.0834 ^c	0.310 ± 0.0912 ^b
t _½ (h)	37.2 ± 7.19 ^a	36.0 ± 7.78 ^b	30.0 ± 7.56 ^c	28.9 ± 6.84 ^b

Values are means ± SD, except median (range) for t_{max} and t_{lag}

NA: not applicable

N=18, except ^aN = 17, ^bN=16 and ^cN=15

Source: Table 13 and Table 14

b. Distribution: HRA2914-427 (table 11 on protein binding and plasma components binding)

Ulipristal acetate is highly bound in blood and plasma (4.86% to blood cells and 94.09% to plasma proteins), with a free fraction (fu) just above 1%. In plasma, ulipristal acetate is mainly bound to α-acid glycoprotein (AAG), human serum albumin (HSA), high density lipoprotein (HDL) and low density lipoprotein (LDL). The total protein binding remained constant over the concentration range tested despite saturable binding to AAG.

Table 11 Relative binding of ulipristal acetate to blood cells and human plasma proteins

Test system	Ulipristal acetate, μM (ng/mL)	Simulated blood distribution (%)
Unbound fraction (fu)		1.05
Bound Fraction		98.95(4.86 + 94.09)
- To blood cells	0.04-22 (19-10500 ng/mL)	4.86
- To plasma proteins	0.02-18.1 (9.5-8600 ng/mL)	94.09
% binding to individual plasma proteins		Σ 94.09
-HSA with NEFA (37.31 g/mL) (HSA/NEFA=1.44)	0.02-18.1 (9.5-8600 ng/mL)	15.51
-AAG (1 g/L)	0.02-15.7 (9.5-7500 ng/mL)	28.99
-GG (11.5 g/L)	0.02-9.5 (9.5-4500 ng/mL)	0.43
-VLDL (0.5 g/L)	0.007-7.3 (3.3-3500 ng/mL)	0.47
-LDL (3 g/L)	0.02-20.7 (9.5-9800 ng/mL)	19.26
-HDL (3.5 g/L)	0.02-20.6 (9.5-9800 ng/mL)	29.44

c. Metabolism

Ulipristal acetate was metabolised to two metabolites in human liver microsomes. No significant metabolism was observed in the absence of β -NADPH, suggesting a role for cytochrome P450 in the metabolism of ulipristal acetate (HRA2914-429). In studies with recombinant human cytochrome P450 isoenzymes, the metabolism of ulipristal acetate was shown to be predominantly mediated by CYP3A4 (HRA2914-430).

Ulipristal acetate is metabolized by N-demethylation to yield the monodemethylated (CDB 3877) and didemethylated (CDB 3963) derivatives. CDB 3877 has a similar hormonal receptor binding profile to ulipristal acetate itself, although less potent, and CDB 3963 is less potent still. In vivo, CDB 3877 was approximately 4-fold less active than ulipristal acetate in the anti-Clauberg test after oral dosing whilst CDB 3963 did not show any activity in the anti-McGinty test (anti-Clauberg and anti-McGinty tests are animal models of anti-progestogenic activity).

1. Animal

a. Elimination

Investigation in cynomolgus monkeys using radiolabeled ulipristal acetate administered by oral or intravenous routes showed the feces to be the main route of excretion.

Table 12 Excretion of radioactivity following oral and intravenous administration of 5 mg/kg of ¹⁴C-ulipristal acetate to cynomolgus monkeys

Excreta	% of administered dose	
	Oral dosing	Intravenous dosing
Urine	6.27	7.31
Faeces	44.67	66.90
Cage wash	11.80	1.48
Cage debris	6.96	0.82
Carcass	-*	1.22
Total recovery	69.71	78.42

TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Most findings in general and reproductive toxicity studies were related to its mechanism of action as a modulator of progesterone receptors, with antiprogestosterone activity observed at exposures similar to therapeutic levels.

Repeated dose toxicity

The chronic toxicity studies comprised exposure to ulipristal acetate by oral administration in rats and monkeys for 6 months. The main findings from these studies are summarized in Table 13.

Table 13 Summary of key findings in the 6-month toxicology studies in rats and monkeys.

Species	Study Design	Main findings
Rats	6 months, 0, 1, 5, 25 mg/kg/d, oral dosing	Mid and high dose levels: increased bodyweight and food consumption; clinical signs: masses in axillary region that proved to be galactoceles cysts; hematological changes : increased white cell, lymphocyte and neutrophils; reduced erythrocyte numbers, haematocrit and haemoglobin; biochemical changes : reduced sodium, chloride; increased globulin, total protein and cholesterol; macroscopic findings increased liver and adrenal weights and decreased ovaries, uterus and thyroid weights; histological changes : adrenal cortical and liver hepatocyte hypertrophy, ovarian follicular cysts and follicular atresia and uterine glandular dilation, pituitary hyperplasia; changes in mammary glands and ovaries also seen at low dose level.
Monkeys	6 months, 0, 1, 5, 25 mg/kg/d, oral dosing	High dose level: Aggressiveness, emesis and watery faeces; decreased lymphocytes counts and increased neutrophils; decreased alanine transferase and cholesterol, increased adrenal weight and decreased thymus weight, mild hypertrophy of adrenal cortex Mid and high dose level : interruption of the menstrual cycle decreased lymphocytes and increased segmented neutrophils; cystic dilatation of the endometrial glands, with one high-dose animal showing mild squamous metaplasia

Toxicology studies in the rat and monkey did not identify any evidence of overt toxicity following repeated oral administration. The effects of ulipristal acetate were the consequence of disruption of the hypothalamic-pituitary-adrenal axis and reproductive systems which manifested as changes in the pituitary, adrenal and mammary glands as well as in the ovary and uterus, together with increases in serum levels of corticosterone and prolactin. The exception would appear to be the observed effects on the liver – increased weight and hepatocyte hypertrophy – at the high doses in the rat study, but this is likely to be an adaptive response to the increased metabolic load imposed by

daily administration of ulipristal acetate. Treatment-related changes were seen at all dose levels in the rat study and it was not possible to determine a NOAEL. In the monkey study the NOAEL was 25 mg/kg/day.

Genotoxicity studies

Genotoxicity studies have shown no evidence of mutagenic potential.

Carcinogenicity studies

Carcinogenicity studies with ulipristal acetate have not been conducted.

Reproduction studies

Reproductive studies were conducted in both rats and rabbits, using oral route of administration. The NOELs for development toxicity were 0.1mg/kg/day and 0.3 mg/kg/day in rats and rabbits, respectively. Doses of 3 and 10 mg/kg/day reduced the pregnancy rate to 20 and 0% in both species. Doses of ~1 mg/kg/day in rabbits and ≥ 0.3 mg/kg/day in rats increased post-implantation loss. In utero exposure to any dose of ulipristal acetate during gestation did not lead to increases in fetal malformations, skeletal anomalies or other developmental toxicity in surviving fetuses, including the fertility of surviving offspring. Exposure to ulipristal acetate (>2 mg/kg/day) late in gestation in rats led to fetal loss.

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/m^2). 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.

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.

PART III: CONSUMER INFORMATION

^{PR} ella[®]
ulipristal acetate tablet

This leaflet is part III of a three-part "Product Monograph" published when ella[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ella[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Use ella[®] within 120 hours or 5 days to help reduce your chances or prevent pregnancy after:

- known or suspected birth control failure. Examples include missed contraceptive pills or a condom breaking or slipping
- unprotected sex (you did not use any birth control)

ella[®] is not for regular use as a contraceptive.

What it does:

ella[®] is an emergency or **back-up** method of preventing pregnancy.

ella[®] may stop or delay the release of an egg from the ovary.

When it should not be used:

- If you are allergic to ulipristal acetate,
- If you are allergic to the non-medicinal ingredients, or the container
- If you are pregnant or suspect a pregnancy.

What the medicinal ingredient is:

Ulipristal acetate

What the nonmedicinal ingredients are:

Croscarmellose sodium, lactose monohydrate, magnesium stearate, and povidone K30.

What dosage forms it comes in:

Tablet, 30 mg

WARNINGS AND PRECAUTIONS

It is very important that you have a reliable form of birth control that is right for you.

ella[®] is not indicated for regular birth control.

ella[®] does not prevent pregnancy in every case.

ella[®] is only effective for one episode of unprotected sex. Right after using ella[®], you are again able to get pregnant. To prevent pregnancy, you should continue your regular method of contraception as usual or you can start to use regular birth control. However, ella[®] may make your regular hormonal birth control method less effective. This lasts for the amount of time between taking ella[®] and your next period. For the rest of your menstrual cycle, it is important that you use a barrier method of birth control every time you have sex. An example is a condom.

It is not recommended to use ella[®] twice in the same menstrual cycle.

ella[®] is not used to end an existing pregnancy. ella[®] does not interrupt a pregnancy.

ella[®] will not protect you against:

- HIV infection (AIDS)
- other sexually transmitted diseases (STDs)

ella[®] is not recommended if you have severe liver disease.

Before you take ella[®], tell your doctor if your last period was not normal. You may already be pregnant.

After taking ella[®], your menstrual cycle may be early or late. If you are more than 1 week late, you should get a pregnancy test.

Do not breastfeed your baby for one week after taking ella[®]. During this time, it is recommended to pump and discard your breast milk in order to stimulate and maintain lactation.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare provider if you are taking or have recently taken any other medicines, including medicines taken without a prescription.

Other medications or herbal products that you are taking might cause ella[®] to work less well such as St. John's wort.

Drugs that may interact with ella[®] include:

- phenytoin (used for treatment of epilepsy)
- rifampin, rifampicin (antibiotic treatment of tuberculosis)
- phenobarbital (used for treatment of epilepsy)
- carbamazepine (used for treatment of epilepsy)
- barbiturates (used for treatment of epilepsy)

IMPORTANT: PLEASE READ

- bosentan (used for treatment of pulmonary hypertension)
- felbamate (used for treatment of epilepsy)
- griseofulvin (antibiotic used in treatment of certain skin lesions)
- oxcarbazepine (used for treatment of epilepsy)
- topiramate (used for treatment of epilepsy)
- dabigatran etexilate (used to prevent blood clots)
- digoxin (used for treatment of various heart conditions)

ella[®] may reduce how well oral contraceptives work to prevent pregnancy. This includes combined hormonal contraceptives and progestogen-only contraception.

ella[®] should not be used together with emergency contraceptives containing levonorgestrel.

PROPER USE OF THIS MEDICATION

Usual dose:

Follow your doctor's instructions very carefully.

Take one tablet by mouth as soon as possible within 5 days (120 hours) after unprotected sex or if you had a birth control failure.

The tablet can be taken with or without food.

If you vomit within 3 hours of taking **ella**[®], contact your healthcare provider immediately in order to take another tablet.

ella[®] can be taken at any time during the menstrual cycle. The use of **ella**[®] as an emergency contraception is only effective for a single episode of unprotected intercourse.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- headache, fatigue, dizziness
- nausea, stomach (abdominal) pain, menstrual pain (dysmenorrhea)
- acne

*This is not a complete list of side effects. For any unexpected effects while taking **ella**[®], contact your doctor or pharmacist.*

HOW TO STORE IT

This package is sealed for your protection. Do not use if torn or broken.

Store at 15-25°C. Store in the original packaging to protect from moisture.

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

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found by contacting the Distributor, Allergan Inc., at 1-800-668-6424.

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