CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022474Orig1s007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**022474/S-07 (ella® ulipristal acetate tablets)**
Submission Type	**Labeling supplement**
Submission Dates	**09/09/2014, 10/22/2014, 01/20/2015**
Reviewer	**Jihong Shon, M.D., Ph.D.**
Team Leader	**Myong-Jin Kim, Pharm.D.**
OCP Division	**Division of Clinical Pharmacology 3**
OND Division	**Division of Bone, Reproductive and Urologic Products**
Sponsor	**LABORATOIRE HRA PHARMA**

1. BACKGROUND

On September 09, 2014, the sponsor submitted a labeling supplement to NDA 022474 (ella®, ulipristal acetate - UPA 30mg; S-07) and proposed revising the multiple sections including, WARNINGS AND PRECAUTIONS (section 5), ADVERS REACTIONS (section 6), DRUG INTERACTIONS (section 7), USE IN SPECIFIC POPULATIONS (section 8), CLINICAL PHARMACOLOGY (section 12), and NONCLINICL TOXICOLOGY (section 13) of the physician labeling. The proposed major changes pertain to pharmacodynamics (PD) interactions between UPA and progestin-containing hormonal contraceptive (HC), *in vitro* drug interaction potential with drug transporters, post-marketing experience in adolescents, and carcinogenicity in animal models. To support these changes, the sponsor submitted the followings: 1) the clinical study reports of PD interactions with the HCs; 2) the study reports of *in vitro* experiments of drug transporters; 3) the study reports of carcinogenicity and assay method validation in animals; 4) the tracked change and clean version of physician labeling. Two Information Requests (IR) were sent to the sponsor to request the annotated labeling (October 16, 2014) and to clarify the source supporting the label update (January 14, 2015). Subsequently, the sponsor submitted the responses on October 22, 2014 and January 20, 2015.

2. SUMMARY of REVIEW and RECOMMENDSTION:

This clinical pharmacology review pertains to drug interaction potential and additional PD information for ella: (1) PD interaction potential between ella® and HCs (see 2.1), (2) PD effects when ella® is used during the late follicular phase (see 2.2), and (3) inhibitory effect of UPA on drug transporters (see 2.3).

2.1 PD interaction potential between ella® and progestin-containing HCs

Given that UPA's efficacy may be compromised by subsequent intake of a HC, the sponsor proposed adding a statement about a five-day dosing interval before initiating a HC in order to preserve the ability of ella® to delay ovulation in a woman seeking emergency contraception. This reviewer agrees that a probable or possible interaction between ella® and a progestin-containing HC can occur. In particular, the inhibitory effect of ella® on ovulation may be undermined when a progestin-containing

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HC is co-administered. In addition, the PD interaction observed between ella® and a HC containing only desogestrel (DSG) suggests that a prior administration of ella® may compromise the contraceptive effect of HCs containing a progestin component.

The proposed labeling about a five-day dosing interval between ella® and a progestin containing HC and additional precautionary statement to prevent pregnancy after ella® and a HC intake is acceptable. In particular, when considering UPA's efficacy duration (for at least 5 days in postponing follicular rupture when taken before peak of lutenizing hormone) and UPA and its active metabolite's half-life (around 30 hours: 4~5 days after intake of ella® will reach more than 90% elimination of both), the recommendation of a five-day dosing interval is reasonable. However, this reviewer recommends the following revisions: 1) specify a progestin component of HC in the descriptions in relation to this PD interaction potential, 2) include a summary of PD interaction study results and move the information from section 12.3 (Pharmacokinetics) to section 12.2 Pharmacodynamics, and 3) minor revisions (wordings, headings, and cross-reference section numbers).

2.2 The PD effect of ella® in the later follicular phase of menstrual cycle

Based on the published reports, the sponsor proposed adding the PD information regarding the effect of ella® in postponing follicular rupture when taken at the late follicular phase. In this regard, a cross-comparison of UPA, levonorgestrel (LNG)-containing emergency contraceptive and placebo is proposed in section 12.2 Pharmacodynamics.

The current proposal is not acceptable because this comparative result was not derived from a well-designed clinical study to assess a rigorous efficacy comparison of ella® with the comparators. However, the PD data from the UPA arm may add a value. Therefore, the reviewer recommends that only the PD results of UPA are included in the physician labeling. In addition, ella® intake did not postpone the follicular ruptures when it was administered on the day of lutenizing hormone (LH) peak. This observation should be included in the same section (12.2).

2.3 *In vitro* interaction potential with drug transporters

The sponsor submitted two *in vitro* study reports to assess the inhibitory potential of UPA on efflux and to update transporters including BSEP, BCRP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2. The screening study showed that UPA did not have a significant inhibition potential on all transporters at the tested concentrations. Additional *in vitro* study to determine the inhibition potential of UPA on BCRP suggested that UPA may have a clinical relevant interaction potential in the intestinal level which is anticipated after taking a dose of UPA (30 mg) as ella®. However, a clinically relevant drug interaction occurs unlikely considering its single dose treatment regimen.

Because no clinical relevant interactions are anticipated, this reviewer recommends that interaction potential of UPA on cytochrome P450 enzymes and transporters should be described in section 12.3 (Pharmacokinetics) instead of what the sponsor has proposed in section 7.3 (Effects of ella on Co-Administered Drugs).

3. THE INDIVIDUAL STUDIES

Reference ID: 3702704

3.1 The PD interaction studies of ella® with a progestin containing HCs

(1) HRA2914-550 study

- **Title:** A prospective, randomized, double-blind parallel-arm, placebo controlled study to assess the effects on ovarian activity of a combined oral contraceptive pill when preceded by the intake of ellaOne®(UPA 30 mg) or placebo.

- **Objectives:** The primary objective was to compare the effects of mid-cycle initiation (known as "quick starting") of a combined oral contraceptive pill (COCP) on follicular growth and hormonal parameters after UPA 30mg or placebo intake. The secondary objective was to compare the effects of quick starting a COCP on menstrual bleeding patterns and tolerability after UPA 30mg or placebo intake.

- **Study scheme**: a double blind, randomized, placebo-controlled trial in healthy female subjects.

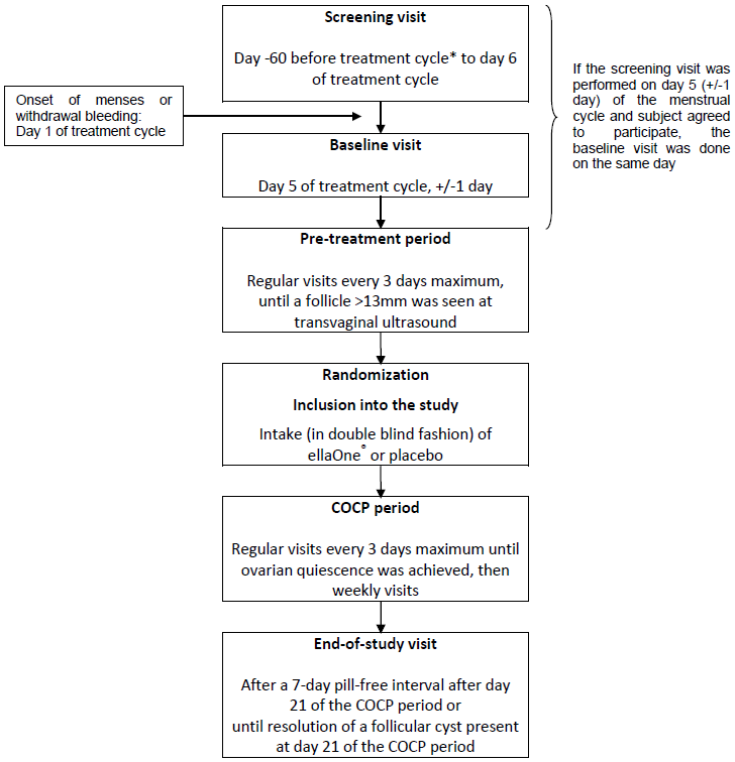

Figure 1. Study scheme

- **Treatments**: Either one tablet of UPA 30 mg or placebo was administered to women with water on day 1 and one tablet of Microgynon 30® (30µg ethinyl estradiol / 150µg LNG) was administered once daily from day 2 for 21 consecutive days.

- **Major criteria of subject selection**:
  - 18-35 years old and BMI < 30 Kg/m2
  - Not at risk of pregnancy
  - No use of hormonal contraception method
  - Regular menstrual cycles

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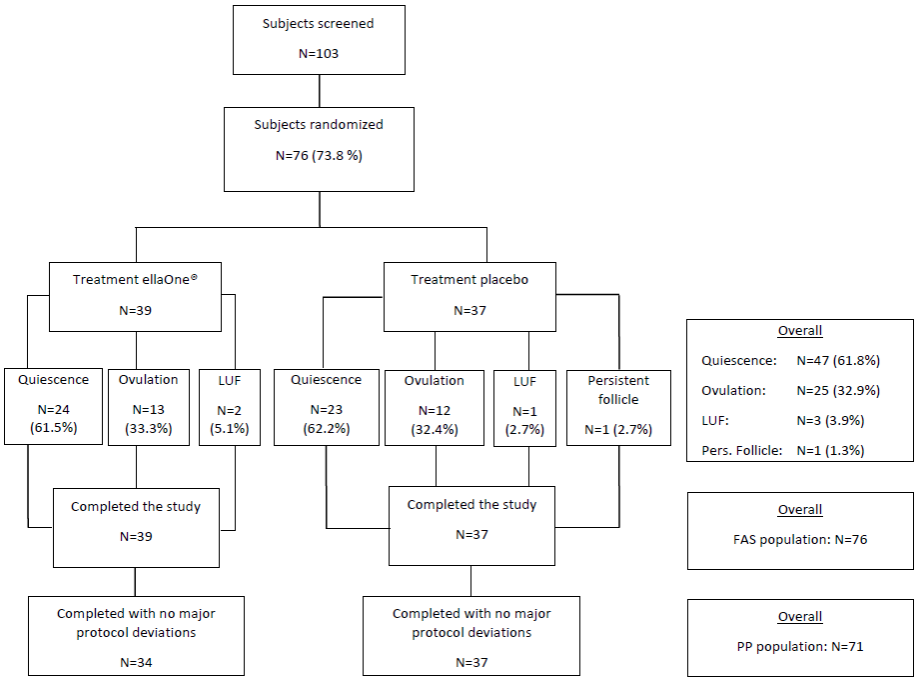
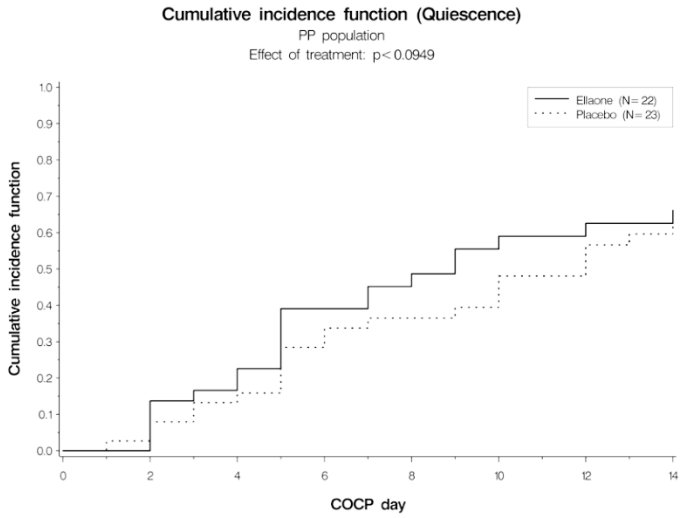
- Dominant follicle size > 13mm observed at day 18 (± 1 day) during the pretreatment period

· **Evaluation**:
- Pharmacodynamics: Follicular growth using transvaginal ultrasonography (TUV) and hormonal parameters (progesterone, estradiol and FSH)
- Achievement of ovarian quiescence: Hoogland score ≤ 3 (follicular diameter and concentrations of estradiol and progesterone)
- Safety: Laboratory parameters, vital signs, occurrence of adverse events, vaginal bleeding pattern and TUV.

- **Results**:



Subject disposition



Cumulative incidence function (Quiescence) – Per protocol population

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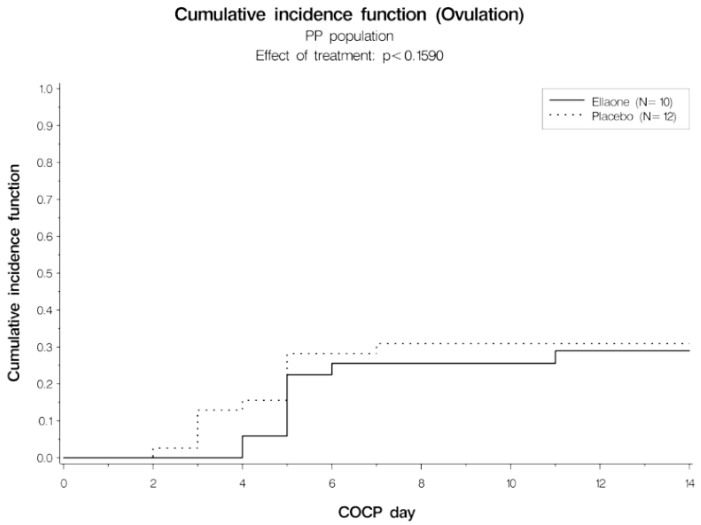
The time to reach quiescence was similar between the UPA (ellaOne®) and the placebo groups. The median time to quiescence was 5 days for the UPA group and 6 days for the placebo group. Seventeen (17) subjects (70.8%) in the UPA group and 14 subjects (60.9%) in the placebo group reached quiescence on Day 7 of the COCP. For both groups, all subjects reached quiescence by Day 14 of the COCP period.

Descriptive statistics (mean±SD) for follicle and endocrine end points - Quiescence

Population	Treatment	N	Peak diameter (mm)	Peak Estradiol (nmol/L)	Peak Progesterone (nmol/L)	Peak FSH (UI/L)
FAS population	ELLAONE®	24	17.48 (5.53)	0.3949 (0.1665)	1.55 (0.89)	5.20 (1.52)
	PLACEBO	23	20.58 (8.48)	0.5187 (0.3836)	1.49 (0.91)	4.13 (1.10)
PP population	ELLAONE®	22	17.73 (5.72)	0.4144 (0.1597)	1.55 (0.92)	5.03 (1.47)
	PLACEBO	23	20.58 (8.48)	0.5187 (0.3836)	1.49 (0.91)	4.13 (1.10)
Specificity population	ELLAONE®	24	17.48 (5.53)	0.3949 (0.1665)	1.55 (0.89)	5.20 (1.52)
	PLACEBO	23	20.58 (8.48)	0.5187 (0.3836)	1.49 (0.91)	4.13 (1.10)



Cumulative incidence function (Ovulation) - PP population

Descriptive statistics (mean±SD) for follicle and endocrine end points - ovulation

Population	Treatment	N	Peak diameter (mm)	Peak Estradiol (nmol/L)	Peak Progesterone (nmol/L)	Peak FSH (UI/L)
FAS population	ELLAONE®	13	18.75 (2.35)	0.7448 (0.2444)	11.40 (11.28)	3.85 (0.96)
	PLACEBO	12	16.98 (1.70)	0.8016 (0.2422)	12.13 (6.62)	6.28 (2.64)
PP population	ELLAONE®	10	18.24 (1.35)	0.7433 (0.2573)	8.23 (9.22)	3.97 (1.02)
	PLACEBO	12	16.98 (1.70)	0.8016 (0.2422)	12.13 (6.62)	6.28 (2.64)
Specificity population	ELLAONE®	12	18.78 (2.45)	0.7198 (0.2372)	12.17 (11.42)	3.92 (0.97)
	PLACEBO	11	16.85 (1.71)	0.7556 (0.1915)	10.80 (5.01)	6.29 (2.77)

The rate of ovulation in both groups was comparable to the results of previous report (*Westhoff et al. 2010*). All subjects in the placebo group reached ovulation by COCP day 7, while UPA group did not reached ovulation until day 11. Although the majority of subjects in the UPA group (~90%) ovulated within the first week, most ovulations occurred after day 4 of COCP.

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- **Sponsor's conclusion**: These data indicate that there were no differences between UPA or placebo for the effect of quick-starting a COCP on follicular development. The intake of UPA 30mg has no clinically significant impact on reaching quiescence within 7-10 days after starting COCP.

Reviewer comments

- *ellaOne® (approved and marketed in EU) used in this study is same product as ella® available in the US.*
- *The UPA group did not have any difference in the effect of LNG-containing COC on ovarian activity when compared with the placebo group.*
- *The ovulation in the UPA group tended to be delayed when compared to that in the placebo group. However, the UPA group (33.3%) showed the ovulation rate similar to that observed in the placebo group (32.4%) and the majority of these subjects had reached ovulation within the first week after intake of UPA 30mg. It may imply that the inhibitory effect of ella® on ovulation can be reduced when COC is given after ella® intake.*

(2) HRA2914-5008 study

- **Title:** Prospective, randomized, cross-over, single-blind, placebo controlled study to assess the PD effects, pharmacokinetics (PK), safety and tolerability of one dose of 30mg UPA followed by the administration of 20 days of 75µg DSG.

- **Objectives:** To compare the contraceptive effects (based on the occurrence of ovulation and cervical mucus characteristics) of the three following treatment regimens within the 21-day treatment period- UPA 30mg single dose followed by 75µg DSG per day for 20 days vs UPA 30mg single dose followed by one tablet of placebo per day for 20 days vs one tablet of placebo followed by 75µg DSG per day for 20 days

- **Study design and scheme**: a randomized, cross-over, single-blind, placebo controlled study in healthy female subjects.

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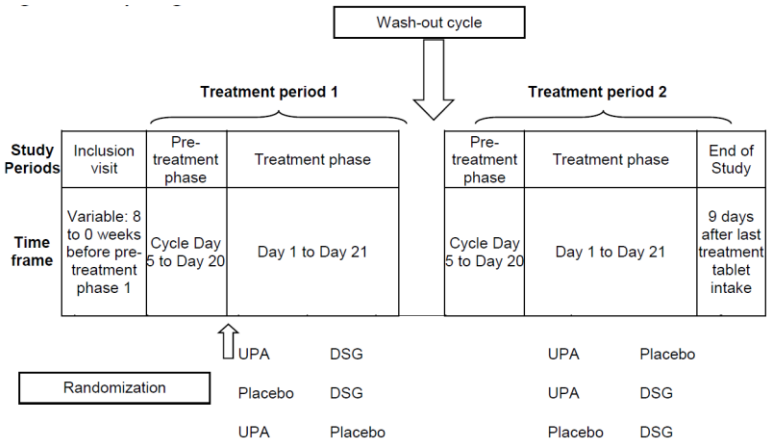

Study design

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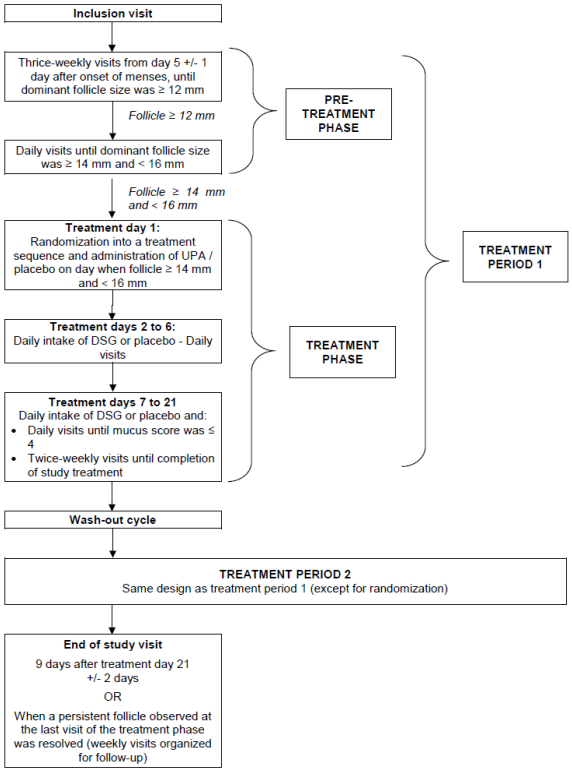
Subjects were randomized to receive either UPA (ellaOne®) or placebo 1, once the dominant follicle size was above or equal to 14 mm and below 16 mm. DSG (75µg) or placebo 2 was started the day after and taken once daily for 20 days.

· **Major criteria of subject selection**:

- Healthy women: 18-35 years old and BMI < 30 kg/m^2
- Not at risk of pregnancy
- No use of hormonal contraception method
- Regular menstrual cycles

· **Evaluation**:

- Assessment of the contraceptive effect using the status of follicular rupture on transvaginal ultrasonography, hormonal classification (progesterone), and cervical mucus classification.
- Contraceptive effect was evaluated as a binary variable (success or failure) based on the occurrence of ovulation and cervical mucus characteristics over the 21-day period of DSG treatment.
- PK: The PK parameters of ulipristal and active metabolite, 11-demethylated ulipristal, were compared between UPA+Placebo (PLB) and UPA+DSG groups. The plasma concentrations of etonogestrel, active metabolite of DSG, were compared before and 2 hours after intake of DSG PLB+DSG and UPA+DSG groups during the first five days of DSG administration.
- Safety: laboratory parameters, vital signs, adverse events, and vaginal bleeding episodes.



Study scheme

- **Results**:

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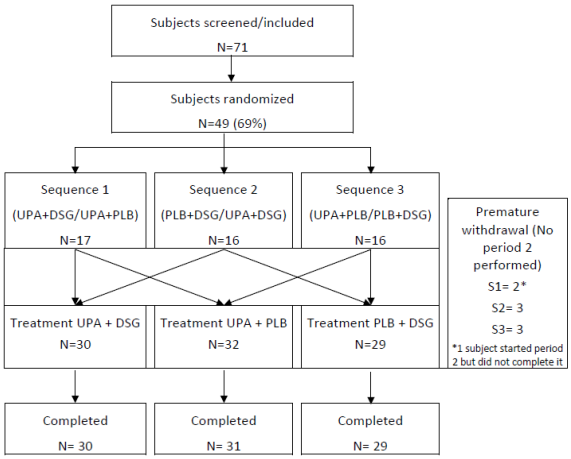
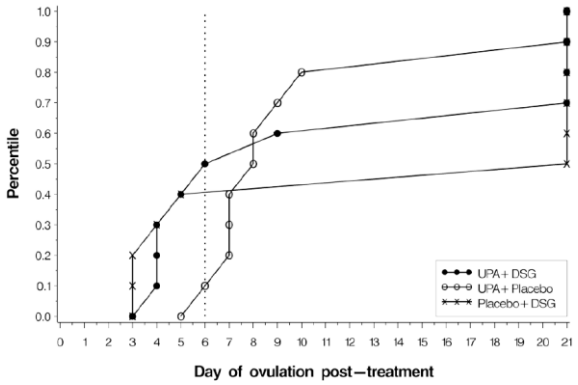


Subject disposition

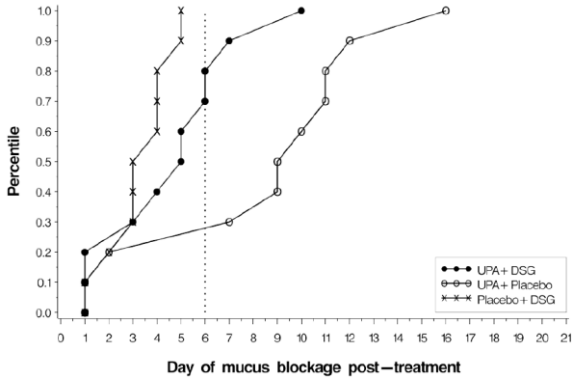
No contraceptive effect and logistic regression estimates
(post-hoc population, all treatment cycles included)

		Measured			Model estimates			
			95% CI				95% CI	
Treatment	n	Rate	Lower	Upper	Predicted rate	Standard Error (SE)	Lower	Upper
UPA+DSG	14	0.483	0.294	0.675	0.4814	0.1205	0.2622	0.7080
UPA+PLB	20	0.690	0.492	0.847	0.7405	0.0998	0.5039	0.8891
PLB+DSG	12	0.414	0.235	0.611	0.4444	0.1174	0.2370	0.6732

* Covariates in the model: center, treatment; p = 0.1220



Cumulative percentage of events of ovulation in all treatment cycles



Cumulative percentage of events, mucus blockage

Estimated time to mucus blockage event.

Comparison Dataset Treatment	Data selection	Model estimates Estimate	95% CI Lower	95% CI Upper	BandC 95% CI Lower	BandC 95% CI Upper
UPA+DSG vs. Placebo+DSG						
Possible ovulation included						
UPA+DSG	UPA+DSG data (sequence 1), Placebo+DSG data (sequence 2 and 3)	3.0	0.0	4.0	0.0	3.0
	UPA+DSG data (sequence 1 and 2), Placebo+DSG data (sequence 3)	4.0	2.0	5.0	2.0	4.0
Placebo+DSG	UPA+DSG data (sequence 1), Placebo+DSG data (sequence 2 and 3)	2.0	2.0	3.0	2.0	2.0
	UPA+DSG data (sequence 1 and 2), Placebo+DSG data (sequence 3)	2.0	0.0	3.0	0.0	2.0
Possible ovulation excluded						
UPA+DSG	UPA+DSG data (sequence 1), Placebo+DSG data (sequence 2 and 3)	3.0	0.0	4.0	0.0	3.0
	UPA+DSG data (sequence 1 and 2), Placebo+DSG data (sequence 3)	4.0	2.0	5.0	2.0	4.0
Placebo+DSG	UPA+DSG data (sequence 1), Placebo+DSG data (sequence 2 and 3)	2.0	2.0	3.0	2.0	2.0
	UPA+DSG data (sequence 1 and 2), Placebo+DSG data (sequence 3)	2.0	0.0	3.0	0.0	2.0

With respect to PK parameters (C_{max} and AUC) of UPA and its metabolite (11-mono-demethylated UPA), there were no significant differences between the UPA+PLB and UPA+DSG treatments. In addition, etonogestrel concentrations measured during the first five days of DSG administration were not different between the UPA+DSG and PLB+DSG treatments.

- **Sponsor's conclusion**: Intake of daily DSG immediately following UPA emergency contraception could compromise the contraceptive action of each individual component, likely due to competition at the site of the progesterone receptor. Such regimen is therefore not suitable for contraception, and precaution should be exercised when both drugs are used by a given woman. In order to preserve the ability of UPA to delay ovulation by at least five days in a woman seeking emergency contraception, a five-day dosing interval before initiating or resuming DSG contraception is recommended.

Reviewer's comments:

- *In the US, the DSG only oral contraceptive is not available, but LNG product (Micronor, norethindrone 0.35mg) as a progesterone only oral contraceptive is still in the market.*
- *Administration of DSG only HC a day after UPA 30 intake appeared to compromise the contraceptive action of both components: The inhibitory effect of UPA on ovulation was reduced when UPA was taken with DSG only HC product compared to when UPA was given alone. The combination treatment (UPA+DSG) group showed a tendency to have a higher incidence of ovulation rate and a lower incidence and slower onset of mucus blockage compared to the DSG only treatment group (estimated median date to mucus blockage: 3-4 days vs 2 days).*
- *These results suggest that a DSG-only oral contraceptive following ella® can undermine its emergency contraceptive effect and co-medication of ella® may compromise the initial contraceptive effect of progestin only products.*

(3) HRA2914-5009 report

- **Title:** Effect of initiation of oral contraceptive pills (combined or progestin only) on ovulation delay induced by UPA for emergency contraception

- **Objectives:** To assess the effect of initiation of daily DSG 75µg or daily ethinyl estradiol 30µg + LNG 150µg (combined oral contraceptive, COC) following mid-cycle UPA 30 mg on the incidence and timing of ovulation through the six days following UPA intake.

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- **Method:**

· The data utilized for this post-hoc analysis originated from two separate PD studies (HRA2914-550 and HRA2914-5008).

· The primary aim was to estimate the proportion of cycles which resulted in ovulation in all groups within six days of treatment, evaluated by logistic regression in which the proportion of women that ovulated in each of the treatment groups (UPA+COC and UPA+DSG) was compared statistically to the proportion of ovulation in the UPA+placebo control group.

· For the comparability of the data from the other studies, the dataset was restricted to subjects who received the COC treatment when the lead follicle was no greater than 16 mm.

- **Results**:

Proportion of ovulation events within the first 6 days of treatment (including regression model estimates).

		Measured			Model estimate			
			95% CI				95% CI	
Treatment	n/N	Rate	Lower	Upper	Predicted rate	SE	Lower	Upper
UPA+COC	8/31	0.258	0.119	0.446	0.249	0.813	0.123	0.441
UPA+DSG	15/29	0.517	0.325	0.706	0.514	0.100	0.3235	0.7008
UPA+Placebo	3/29	0.103	0.022	0.274	0.101	0.0568	0.0311	0.2804

Logistic regression of occurrence of ovulation (until Day 6)

			95% CI			
Contrast name	Estimate	SE	Lower	Upper	T_value	p_value
UPA+DSG vs UPA+Placebo	2.2476	0.7332	0.7900	3.7053	3.07	0.0029
UPA+COC vs UPA+Placebo	1.0882	0.7578	-0.4182	2.5946	1.44	0.1546

- **Sponsor's conclusion**: UPA's normal ability to delay ovulation for 6-8 days following intake is compromised by subsequent intake of a hormonal contraceptive, whether it is a combined oral COC or a pill containing only a progestin (DSG), presumably due to competition at the site of the progestin receptor.

Reviewer's comments:

- *The UPA+COC group showed a higher proportion of ovulation within the six days after intake of UPA than the UPA+Placebo group, but this difference was not statistically different. However, the effect of UPA to postpone ovulation is compromised significantly by intake of DSG only oral contraceptive (UPA+Placebo vs. UPA+DSG).*
- *This assessment demonstrates that the prevention effect of ella® on follicular rupture as a major mechanism of action for emergency contraception can be undermined by a subsequent administration of regular oral contraceptives. However, this result came from a cross-comparison of two separate clinical trials and the comparison between UPA+COC and UPA+Placebo did not reach a statistical significance (p=0.1546).*

3.2 The effect of ella® in the late follicular phase

Reference ID: 3702704

(1) HRA2914-576: analysis report of pooled data of emergency contraception regimens
(Brache V1, Cochon L, Deniaud M, Croxatto HB Contraception 2013;88:611-8.)

- **Title:** Ulipristal acetate prevents ovulation more effectively than LNG- Analysis of pooled data from three randomized trials of emergency contraception regimens (*Brache et al. 2013*)

- **Data analysis method:** Raw data from three PD studies with similar methodology were pooled to allow direct comparison of UPA, LNG and LNG+meloxicam's ability to prevent ovulation when administered orally in the advanced follicular phase, with a leading follicle of ≥18 mm.

- **References:**
  - Croxatto et al. Pituitary-ovarian function following the standard LNG emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. Contraception 2004;70:442–50.
  - Massai et al. Forcelledo ML, Brache V, Tejada AS, Salvatierra AM, Reyes MV, et al. Does meloxicam increase the incidence of anovulation induced by single administration of levonorgestrel in emergency contraception? A pilot study. Hum Reprod 2007;22:434–9.
  - Brache et al. Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture. Hum Reprod 2010;25:2256–63.

- **Results:**

Proportion of unruptured dominant follicles 5days after treatment intake according to LH status.

	Placebo n=50	LNG n=48	LNG + Meloxicam n=31	Ulipristal acetate n=34
Tx before LH surge	0.0%	25.0%	55.6%	100%
(n)	16	12	9	8
Tx after LH surge but before LH peak	10.0%	14.3%	38.5%	78.6%
(n)	10	14	13	14
Tx at LH peak	4.2%	9.1%	22.2%	8.3%
(n)	24	22	9	12

- **Sponsor conclusion:** Ovulation can still be interrupted by emergency contraceptives even when it is imminent. UPA is the most effective option at that time of the cycle because it is able to delay ovulation for at least five days in a higher proportion of women than LNG.

Reviewer's comments:
- *This assessment analyzed the results pooled from three separate exploratory studies. The studies had a limited number of subjects.*
- *The analysis showed that administration of UPA 30mg appears to be relatively more effective to prevent ovulation for at least 5 days following treatment in the late follicular stages (before LH surge and when it started to rise).*
- *However, UPA was not effective in postponing ruptures when administered on the day of LH peak.*

(2) PD study report of UPA
This is a summary about the study of ella® used for above analysis report.

Reference ID: 3702704

Study title	Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture
Reference	Hum Reprod. 2010;25:2256-63 (authors: Brache V1, Cochon L, Jesam C, Maldonado R, Salvatierra AM, Levy DP, Gainer E, Croxatto HB.)
Study design	· A double-blind, crossover, randomized study · 35 women · UPA (30 mg) vs placebo cycle · Serial blood sampling for LH, E2, and PG · Follicular monitoring by ultrasound (before and for 5 days following treatment) · Subgroups in relation to LH levels
Study results	**Table I** LH status and mean LH levels (U/l) in women at time of treatment with UPA or placebo in a study of the capacity of UPA to block follicular rupture. **Table III** Inhibition of follicular rupture at 5 days after treatment administration, stratified by LH status at time of treatment.

Table I LH status and mean LH levels (U/l) in women at time of treatment with UPA or placebo in a study of the capacity of UPA to block follicular rupture.

	UPA		Placebo	
	n (1st/2nd cycle)	LH (Mean ± SD)	*n* (1st/2nd cycle)	LH (Mean ± SD)
Treatment before LH surge onset	8 (5/3)	4.1 ± 1.8	12 (6/6)	4.8 ± 1.7
Treatment after LH surge onset but before LH peak	14 (7/7)	10.0 ± 2.6	6 (2/4)	11.8 ± 2.3
Treatment after LH peak	12 (5/7)	54.8 ± 21.3	16 (9/7)	47.8 ± 23.5

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

	UPA *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.

3.3 Assessment of inhibitory potential of ella® on efflux and uptake transporters

(1) HRA2914-489: in vitro screening of efflux and uptake and efflux transporters

- **Study title**: Assessment of potential substrate and inhibitor of PGL4001 (UPA) of efflux (BCRP and BSEP) and uptake (OCT1, OCT2, OAT1, OAT3, OATP1B1 and OATP1B3) transporter

- **Method and results**: The uptake transporter substrate and inhibitory potential of ulipristal was evaluated in a cellular uptake assay using a transporter-specific probe substrate. The experimental conditions and results are summarized in the following table.

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Assessment of potential substrate and inhibitor of ulipristal on efflux and uptake transporters

Transporter	Tested UPA concentration	Cell system	Substrate and concentration	Results	Interpretation
Substrate assessment					
OATP1B1	0.5, 2, 10 μM	Transfected HEK293 cells	Atorvastatin 0.15 μM	Uptake ratio < 2.0	No substrate potential
OATP1B3	0.5, 2, 10 μM	Transfected HEK293 cells	Atorvastatin 0.15 μM	Uptake ratio < 2.0	No substrate potential
Inhibitor assessment					
BSEP	0.288~70 nM	BSEP vesicles	^{3}H-taurocholic acid 1 μM	All tested inhibition < 50%	No significant inhibition
BCRP	4 μM	CPT-P1 cells	Cladribine 10 μM	% inhibition = 25.3%	No significant inhibition
OATP1B1	1 μM	Transfected HEK293 cells	Atorvastatin 0.15 μM	% inhibition = 14.1%	No significant inhibition
OATP1B3	1 μM	Transfected HEK293 cells	Atorvastatin 0.15 μM	% inhibition = 3.85%	No significant inhibition
OCT1	1 μM	Transfected HEK293 cells	1-Methyl-4-phenylpyridinium iodide (MMP^{+}) 5μM	% inhibition = 1.27%	No significant inhibition
OCT2	0.07 μM	Transfected HEK293 cells	MMP^{+} 5μM	% inhibition = 6.88%	No significant inhibition
OAT1	0.07 μM	Transfected HEK293 cells	Para-aminohippurate (PAH) 10μM	No inhibition	No significant inhibition
OAT3	0.07 μM	Transfected HEK293 cells	Furosemide 5μM	No inhibition	No significant inhibition

Reviewer's comments:

- *The in vitro experimental system to assess the transporter substrate and inhibitory potential is acceptable.*
- *The control probe inhibitors showed a high inhibition potential on the transport of probe substrates.*
- *The tested concentrations of UPA were selected based on the guidences of two regulatory agencies (FDA and EMA) for in vitro transporter study. The tested UPA concentration (4μM, approximately one tenth of $[I]_2$) for the BCRP inhibitor assessment was determined based on the $[I]_2$ value (42.1μM) obtained after a studied dose for uterine fibroids (5mg per day). When considering dose of ella® (UPA 30mg) tablet for emergency contraception, the corresponding $[I]_2$ is about 250 μM according to the information provided by the sponsor. It indicates that higher ulipristal concentrations should be tested to assess an inhibitory potential of BCRP in the intestine level.*
- *The results showed that ulipristal does not have a significant inhibition potential on BSEP, BCRP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, or OCT2 at the tested UPA concentrations.*

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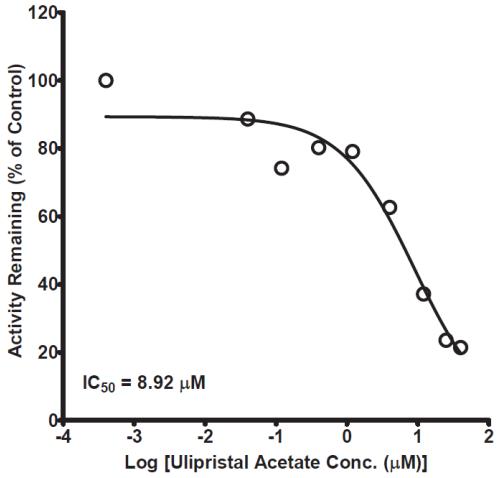
(2) HRA2914-490: assessment of inhibitory potential of ella® on BCRP transporter

- **Study title**: Determining the inhibition potential of UPA for BCRP transporter

- **Synopsis of study**:

Study objective	To assess if ulipristal is a possible BCRP inhibitor using an IC_{50} approach.
Experimental conditions	· Cell system: CPT-P1 cells (Puromycin was added to keep the selection pressure for P-glycoprotein knockdown). · Substrate: cladribine 5 μM · Control compound: Ko143 · Tested ulipristal concentration: 0.04 0.12, 0.4, 1.2, 4, 12, 25, and 40 μM · A unidirectional manner (basolateral-to- apical)
Results	Effect of UPA on BCRP 
Sponsor conclusion	UPA showed inhibitory effect on BCRP under current test conditions with an IC_{50} value of 8.92 μM. When used for emergency contraception as ella® tablet containing UPA 30mg, the corresponding $[I]_2$ is about 250 μM. Because the IC_{50} of UPA is 8.92 μM, the calculated $[I]_2/IC_{50}$ (250 μM / 8.92 μM) is about 28. The clinical relevance of this observation needs to be evaluated in the context of a single dose intake.

***Reviewer comments**:*

- *The control inhibitor, Ko143, showed an potent inhibition on the transport of probe substrate, cladribine.*
- *The various concentrations of UPA were tested. The concentration anticipated in the intestine after taking Ella® was considered. The in vitro experimental system to assess an inhibitory potential of ulipristal on BCRP are acceptable.*
- *Ulipristal acetate showed a concentration-dependent inhibitory potency on the BCRP transport activity of cladribine with an IC_{50} value of* 8.92 μM.

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- *Given that the $[I]_2$ is about 250μM after taking ella® tablet, the calculated value of $[I]_2/IC_{50}$ appeared to be higher than 10, which indicates the clinical relevant interaction potential (FDA DDI guidance). However, clinically relevant drug interaction is unlikely anticipated when considering the relative inhibitory potency of ulipristal on BCRP and its single dose treatment regimen.*

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4. LABEL RECOMMENDATON

Based on above findings, the proposed label updates can be reconstructed as follows:

Proposal from the sponsor	Recommendation
HIGHLIGHTS OF PRESCRIBING INFORMATION **----------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 can do so no sooner than 5 days after intake of ella. (5.5) • Ectopic pregnancy: …..	***<Correction of a word>*** • 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 ~~can~~ do so no sooner than 5 days after intake of ella. (5.5)
FULL PRESCRIBING INFORMATION **5.5 Fertility Following Use** A rapid return of fertility is likely following treatment with **ella** for emergency contraception~~;~~ (b) (4) [redacted]	***<Acceptable>***
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 hormonal contraception 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* (b) (4)	***<Addition of a progestin component and revision of the cross-reference>*** Because **ella** and the progestin component of hormonal contraception 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)* (b) (4) [redacted]

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Proposal from the sponsor	Recommendation
7.1 Changes in Emergency Contraceptive Effectiveness Associated with Co-Administration of Other Products Drugs or herbal products that……	
Hormonal contraceptives: (b) (4) progestin-containing contraceptives may impair the ability of **ella** to delay ovulation *[see Warnings and Precautions (5.5)* (b) (4) Avoid co-administration of **ella** and hormonal contraceptives. If a woman wishes to (b) (4) 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.	***<Acceptable, minor revision>*** Hormonal contraceptives: (b) (4) progestin-containing contraceptives may impair the ability of **ella** to delay ovulation *[see Warnings and Precautions (5.5) and Pharmacodynamics(12.2)* (b) (4) Avoid co-administration of **ella** and hormonal contraceptives. If a woman wishes to use 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.
7.3 Effects of ella on Co-Administered Drugs *In vitro* studies demonstrated that **ella** does not induce or inhibit the activity of cytochrome P450 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 (12.3)*].	***<This part was moved to Section 12.3. because it does not have any clinical relevance>***
Hormonal contraceptives: (b) (4) **ella** may impact the effect of hormonal contraceptives. (b) (4) Therefore, if a woman wishes to use hormonal contraception after using **ella**, subsequent acts of intercourse (b) (4) next menstrual period.	***<Acceptable, minor revision and rearrangement>*** Hormonal contraceptives: (b) (4) — **ella** may impact the effect of the progestin component of hormonal contraceptives. (b) (4) Therefore, if a woman wishes to use hormonal contraception after using **ella**, subsequent acts of intercourse should be protected by a reliable barrier method until the next menstrual period *[see Warnings and Precautions (5.5) and Pharmacodynamics (12.2)].*
BCRP (Breast Cancer Resistance Protein) transporters: *In vitro* data indicate that ulipristal acetate may be an inhibitor of BCRP at the intestinal level. The effects of (b) (4)	***< This part was moved to Section 12.3. because it does not have any clinical relevance>***

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Proposal	Recommendation
12 CLINICAL PHARMACOLOGY **12.2 Pharmacodynamics** Ulipristal acetate …… 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. (b) (4)	***<Acceptable>***
Pharmacodynamic data show that administration of ella in the late follicular phase, before the luteinizing hormone surge, (b) (4)	***<Deletion of the comparative description, and rephrased with only the result of ella>*** Pharmacodynamic data show that administration of ella to 34 women in the late follicular phase, (b) (4) 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. (b) (4) .
	<Moved from the section 12.3 and rephrased with concrete data from the supporting study report> **Effects of Hormonal Contraceptives after ella intake:** When a combined oral contraceptive pill (COC) containing ethinyl estradiol 30 µg + levonorgestrel 150µg was started the day after **ella** intake during the follicular phase, **ella** did not interfere with the COC's ability to induce ovarian quiescence, and the incidence of ovulation was similar between the group who received ella plus the COC and the group who received a placebo plus the COC.*[see Warnings and Precautions (5.5) and Drug Interactions (7.3)]*. The initiation 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)]*.

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Proposal	Recommendation
12 CLINICAL PHARMACOLOGY	
12.3 Pharmacokinetics	
Drug interactions	
……	***<Moved from the section 7.3. >***
	In vitro studies demonstrated that **ella** does not induce or inhibit the activity of cytochrome P450 enzymes.
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.	***<Reconstructed with the parts in the section 7.3 and addition of no clinical relevance>*** **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 and substrates of P-pg and BCRP transporters.
Hormonal contraception: When a combined oral contraceptive pill (COCP) 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 COCP's ability to induce ovarian quiescence, but ovulation occurred later in the cycle in some women.*[see Warnings and Precautions (5.5) and Drug Interactions (7.3)].*	***<Moved to the section 12.2>***
The initiation of a desogestrel 75µg-only pill the day after **ella** intake during the follicular phase was associated with a higher incidence of ovulation in the five days following **ella** intake and a slower onset of mucus blockage compared to desogestrel without prior **ella** intake, 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)].*	

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5. REFERENCE

- Brache et al. Immediate pre-ovulatory administration of 30 mg ulipristal acetate significantly delays follicular rupture. Hum Reprod 2010;25:2256–63.
- Croxatto et al. Pituitary-ovarian function following the standard LNG emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. Contraception 2004;70:442–50.
- Massai et al. Forcelledo ML, Brache V, Tejada AS, Salvatierra AM, Reyes MV, et al. Does meloxicam increase the incidence of anovulation induced by single administration of levonorgestrel in emergency contraception? A pilot study. Hum Reprod 2007;22:434–9.
- Westhoff CL, Torgal AH, Mayeda ER et al. Ovarian suppression in normal-weight and obese women during oral contraceptive use: a randomized controlled trial. Obstet Gynecol 2010;116:275-83.

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/s/

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02/13/2015