4 December 2014, rev 1
EMA/73099/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ellaOne

International non-proprietary name: ulipristal acetate

Procedure No. EMEA/H/C/001027/II/0021

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Laboratoire HRA Pharma, SA submitted to the European Medicines Agency on 6 February 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
ellaOne	ulipristal acetate	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.5.b	C.I.5.b - Change in the legal status of a medicinal product for centrally authorised products - All other legal status changes	II

The marketing authorisation holder (MAH) proposed a change in the classification for supply of ellaOne from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription" in the EU. Update of the Product information in line with a non-prescription setting is proposed. The MAH also proposed updates of SmPC sections 4.2, 4.4 and 5.1 based on Repeated use study (Protocol 091015-001/CSR HRA2914-554 - SmPC sections 4.4 and 5.1) and on interim data from the STEella study in post-menarcheal girls and adult women (Protocol 2914-010/ EUDRACT nr 2009-017771-21/ CSR HRA 2914-515 - SmPC sections 4.2 and 5.1). The Package Leaflet and Labelling were proposed to be updated accordingly.
Furthermore the MAH took this opportunity to bring the PI in line with the QRD template version 8 Rev2 .

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 74a of Directive 2001/83/EC - One year of data exclusivity for a change in the legal status classification.

1.2. Steps taken for the assessment

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff

Co-Rapporteur: Kristina Dunder

Submission date:	6 February 2013
Start of procedure:	24 February 2013
Rapporteur's preliminary assessment report circulated on:	28 March 2013
Rapporteur's updated assessment report circulated on:	18 April 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2013
MAH's responses submitted to the CHMP on:	20 September 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 October 2013
Rapporteur's final assessment report on the MAH's responses circulated on:	14 November 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 November 2013
MAH's responses submitted to the CHMP on:	17 January 2014
Revised Request for supplementary information and extension of timetable adopted by the CHMP on:	23 January 2014
MAH's responses submitted to the CHMP on:	19 September 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 October 2014
Rapporteur's final assessment report on the MAH's responses circulated on:	17 November 2014
An Oral explanation took place on:	18 November 2014
CHMP opinion:	20 November 2014
The CHMP adopted a report on the significance of pre-clinical tests or clinical trials in support of a change in the classification of ellaOne from prescription to non-prescription in accordance with Article 74a of Directive 2001/83/EC	20 November 2014
The CHMP re-adopted a revised AR through written procedure	04 December 2014

2. Scientific discussion

2.1. Introduction

EllaOne, containing ulipristal acetate (UPA), is an orally active synthetic progesterone receptor modulator, which acts via high affinity binding to the human progesterone receptor. The product is indicated for emergency contraception (EC) within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

This indication differs from the levonorgestrel-containing emergency contraceptive which is indicated for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method. Levonorgestrel emergency contraception has a non-prescription status in many European countries.

In the current Type II procedure the MAH is requesting a change in the classification for supply of ellaOne from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription". An update of the Product information in line with a non-prescription setting is proposed.
Updates of SmPC sections 4.2, 4.4 and 5.1 are also proposed based on repeated use study (HRA2914-554) and on the STEella study in postmenarcheal girls and adult women (HRA2914-515). Additionally, the contraindication “pregnancy” is proposed to be removed based on available non-clinical and clinical data.

Relevant for the assessment are criteria in Article 71 of Directive 2001/83/EC and the *Guideline on changing the classification for the supply of a medicinal product for human use* (European Commission, 2006 revision). The article 71 and the Guideline on changing the classification for the supply of a medicinal product for human use determine the following four criteria:

1. Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision
2. Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health
3. Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof, the activity and/or side-effects of which require further investigation
4. Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection)

The MAH submitted the following documentation in order to support these changes:

- Clinical Overview
- Clinical Overview Addendum
- Study report HRA2914-554: A Prospective, Open-Label, Multi-Centre Study to Assess the Pharmacodynamics of Repeated Administrations of 30 mg Ulipristal Acetate (UPA)
- Study report HRA2914-555: Pooled phase III safety analysis by age groups, race and region
- Study report HRA2914-558: Analysis of intermenstrual bleeding episodes in studies HRA2914-509 and HRA2914-513
- Study report HRA2914-515: Prospective Observational Single Arm Open-Label Multi-centre Study to Assess the Safety, Tolerability and Efficacy of ellaOne (Ulipristal Acetate) for Emergency Contraception in Postmenarcheal Adolescent Girls and Adult Women
- Technical report HRA2914-648: Retrospective Study to Assess the Outcomes of Pregnancies Exposed to ellaOne at Planned Parenthood Columbia Willamette
- Relevant publications and meta-analyses

2.2. Clinical Pharmacology aspects - Pharmacodynamics

2.2.1. Methods – analysis of data submitted

The MAH submitted the following publication and clinical study report in support of this variation.

2.2.1.1.1. HRA2914-576 (submitted to Contraception, Brache et al., 2013)

This study analyzed pooled data from three studies conducted by the same group of investigators using similar randomized double-blind placebo controlled crossover study designs. The regimens studied were:

- Study 1: levonorgestrel 1.5 mg versus levonorgestrel 0.75 mg versus placebo (Croxatto et al, 2004);

- Study 2: levonorgestrel 1.5 mg plus placebo versus levonorgestrel 1.5 mg plus Meloxicam 15 mg (Massai et al, 2007);
- Study 3: ulipristal acetate 30 mg versus placebo (Brache et al, 2010).

The primary objective was to estimate and compare the different regimens with respect to the proportion of subjects in whom follicular rupture did not occur in the five days following treatment.

Follicular rupture was defined as an abrupt disappearance (or >50% reduction in size) of the leading follicle whose mean diameter was 15–25 mm in the transvaginal ultrasound (TVU) performed on the day before.

A total of 163 cycles were included in the analysis, 50 placebo, 48 levonorgestrel, 31 levonorgestrel + meloxicam, and 34 ulipristal acetate.

Table 1: Proportion of un-ruptured dominant follicles 5 days after treatment intake

	Placebo n=50	Levonorgestrel (LNG) n=48	LNG + Meloxicam n=31	Ulipristal acetate (UPA) 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

RR: Relative Risk of not rupturing from Regimen 1 to Regimen 2
Treatment before surge:
RR (UPA/LNG), 95% CI: 4.0 [1.5-10.7] p=0.0026
RR (PLACEBO/LNG + MELOX), 95% CI: 0.44 [0.21-0.92]
RR (PLACEBO/UPA), 95% CI: Non calculable
Treatment after surge before peak:
RR (UPA/LNG), 95% CI: 5.5 [1.48-20.42] p=0.0018
RR (UPA/PLACEBO), 95% CI: 7.86 [1.20-51.46 p=0.0028

The authors concluded that ulipristal acetate is able to delay follicular rupture for at least 5 days in a significantly higher proportion of women (58.8%) than levonorgestrel (14.8%) when given in the advanced follicular phase, with a dominant follicle of ≥ 18 mm, close to ovulation (p=0.0001). However, ulipristal acetate and levonorgestrel were both not effective when administered on the day of the LH peak.

2.2.1.1.2. HRA2914-554

A study examined the effect of repeated doses of 30 mg ulipristal acetate (weekly or every 5 days for 8 consecutive weeks) on ovulation, menstrual cycle parameters, and safety. 12 and 11 subjects were included in the Q7D and the Q5D treatment arms, respectively.

Safety was assessed by monitoring adverse events (AEs), laboratory safety parameters, vaginal bleeding patterns, endometrial measurements from TVUs, histological and immunological analyses of endometrial biopsies (collected at baseline and after return of menses during the luteal phase in the Q7D treatment arm and within a few days of the last tablet intake in the Q5D treatment arm), presence of cyst-like structures, venous thromboembolic (VTE) risk markers, vital signs, and physical and gynaecological examinations.

Ovulation

Table 2

	Q7D (N=12)	Q5D (N=11)
Number of subjects who ovulated at least once, n (%) [95% CI]	11 (91.7%) [61.5%;99.8%]	8 (72.7%) [39.0%;94.0%]
Total number of ovulations	17	9
Number of ovulations, n (%) [95% CI]		
Never	1 (8.3%) [0.2%;38.5%]	3 (27.3%) [6.0%;61.0%]
Once	5 (41.7%) [15.2%;72.3%]	7 (63.6%) [30.8%;89.1%]
Twice	6 (50.0%) [21.1%;78.9%]	1 (9.1%) [0.2%;41.3%]
Number of tablets administered prior to occurrence of 1st ovulation Mean (SD)	3.4 (2.5)	6.5 (2.7)
Time from the start of treatment to 1st ovulation (days) (Kaplan Meier estimate) Median (Min, Max)	17 (8, 57)	26 (16, 51)

During the treatment period, a total of 26 ovulations occurred in 19 subjects, 17 in the Q7D treatment arm and 9 in the Q5D treatment arm.

- In the Q7D treatment arm, 1 subject never ovulated, 5 ovulated once, and 6 ovulated twice during the 8 weeks of treatment. The mean number of tablets administered prior to first ovulation was 3.4 and the median time from the start of treatment to the first ovulation was 17 days.
- In the Q5D treatment arm, 3 subjects never ovulated, 7 ovulated once, and 1 ovulated twice. The mean number of tablets administered prior to the first ovulation was 6.5 and the median time from the start of treatment to the first ovulation was 26 days.

Hormonal effects

Ovulatory cycles had physiological levels of estradiol (mean follicular phase estradiol 252.2 pmol/L) and progesterone (mean luteal phase progesterone 38.3 nmol/L), and ovulations were followed by normal luteal phases that lasted a mean of 14.8 days. Maximum follicular size at time of rupture averaged at 21.0 mm. In the Q5D treatment arm, ovulatory cycles usually had shorter luteal phase duration than in the Q7D treatment arm (mean 12.3 days versus 16.1 days).

When luteinized unruptured follicles occurred, follicular estradiol and luteal progesterone levels were in physiological ranges, while mean luteal phase duration was increased (overall mean 18.3 days).

Mucus evaluation

In both treatment arms, the mean overall scores for the cervical mucus evaluation (performed during treatment period if follicle ≥15 mm) indicated cervical mucus normally favourable to sperm penetration.

Adverse events

The number and percentage of subjects with related TEAEs are presented by preferred term in the following table.

Table 3

Number (%) of Subjects with Related TEAEs			
Preferred Term	Q7D (N=12)	Q5D (N=11)	Total (N=23)
	Number (%) of subjects		
All	5 (41.7%)	2 (18.2%)	7 (30.4%)
Headache	3 (25.0%)	0	3 (13.0%)
Blood fibrinogen increased	1 (8.3%)	1 (9.1%)	2 (8.7%)
Prothrombin fragment 1+2 level increased	1 (8.3%)	1 (9.1%)	2 (8.7%)
Dizziness	1 (8.3%)	0	1 (4.3%)
Abdominal pain lower	1 (8.3%)	0	1 (4.3%)
Ovarian cyst	0	1 (9.1%)	1 (4.3%)

*Note: "Related" defined as certain, probably, possible or unknown relationship to treatment as assessed by the investigator

Overall, 11 TEAEs with a reasonable possibility of a causal relationship to treatment (certain, probable, possible, relationship as assessed by the investigator) were reported by 7 subjects (30.4%). One subject had a persistent follicle which fulfilled the criteria for classification as a cyst-like structure, and which was reported as a related TEAE of mild severity although not clinically symptomatic in the Q5D treatment arm.

Bleeding pattern

During the treatment period, subjects experienced a mean of 5.8 days of menstrual bleeding and 1 day of unscheduled bleeding per cycle in the Q7D arm, a similar bleeding profile to that observed at baseline. In the Q5D treatment arm, subjects experienced a mean of 4.5 days of menstrual bleeding and 3 days of unscheduled bleeding per cycle. Compared to the baseline profile for this treatment arm, the number of unscheduled bleeding days was slightly increased but the unscheduled bleeding was usually not heavy.

Endometrium

Mean endometrial thicknesses as measured on TVUs at the end of study (luteal phase of post-treatment cycle) were 9.1 mm and 10.4 mm in the Q7D and Q5D treatment arms, respectively. This represented a change of 3.8 mm and 4.3 mm versus baseline follicular phase measurements. The baseline measurement being in early follicular phase immediately after the end of menses, a time when the endometrium is the thinnest, and the end of study measurements were done in the luteal phase after the first return of menses when the endometrium is physiologically thicker. When comparing the endometrial thickness in luteal phase both at baseline and end of study, no difference is observed.

All endometrium biopsies were classified as benign. No endometrial hyperplasia was reported. In the Q7D treatment arm, the endometrium evaluation on biopsy showed physiological features, both at baseline and at the end of treatment (after one post-treatment menstrual bleed). In the Q5D treatment arm, at the end of treatment (within 5 days of the last tablet intake), 5 subjects had physiological endometrial appearance and 5 subjects had a non-physiological endometrial appearance (among which one was reported as typical progesterone receptor modulator-associated endometrial changes [PAECs]).

Conclusion

The effects of UPA 30 mg administered Q7D or Q5D over 8 weeks demonstrated that following an initial period during which follicular activity was delayed but, following 3 to 6 doses, ovulation occurred in a majority of subjects. When ovulation occurred, physiological and hormonal characteristics indicated no abnormalities. No endometrial hyperplasia or malignancy was reported. No safety issues have been detected, indicating that should the product be used more than once in the

same cycle, the safety profile is similar to that of established for a single 30 mg dose. Product labelling nevertheless cautions that EC is not to be used repeatedly and encourages women who repeatedly resort to EC to seek counselling and care for regular contraception.

2.2.2. Discussion and conclusion by the CHMP

2.2.2.1.1. HRA2914-576

The results of this study show that ulipristal acetate is able to delay follicular rupture for at least 5 days in a higher proportion of women than levonorgestrel when given in the late follicular phase, before LH surge and after LH surge but before LH peak. However, on the day of the LH peak ulipristal acetate, similar to levonorgestrel, cannot delay or inhibit ovulation any better than placebo.

Based on this publication, a proposal was made by the MAH to update section 5.1 of the SmPC, in order to better inform healthcare professionals on the mechanism of action of ellaOne.

This is important additional information on the mechanism of action of ulipristal acetate as an emergency contraceptive and therefore the inclusion of the results of this study was agreed by the CHMP.

2.2.2.1.2. HRA2914-554

This study shows that ellaOne initially delays follicular activity. However, none of the regimens (every week or every 5 days for 8 consecutive weeks) inhibited ovulation during the whole period of 8 weeks in the majority of subjects. The CHMP agrees that no safety issues are apparent after repeated administration in the same cycle. The endometrial thickness at the end of the study was comparable to baseline luteal values. Non-physiological receptor modulator-associated endometrial changes were observed in one subject in the Q5D group. This is in line with the findings of the Phase III studies of Esmya for the treatment of uterine fibroids in which subjects received daily 5 or 10 mg ulipristal acetate (EPAR Esmya), and is no reason for concern. In the subjects in the Phase III studies of Esmya PAECs were described in approximately 60% of subjects treated with daily ulipristal acetate. PAECs had returned to baseline level when the follow-up biopsy was performed three months after the end of the 3-month treatment period in the Esmya Phase III studies.

Based on this study, the CHMP agrees with the proposal from the MAH to remove the following warning in section 4.4:

“Repeated administration of ellaOne within the same menstrual cycle is not advisable, as safety and efficacy of ellaOne after repeated administration within the same menstrual cycle has not been investigated.”

It is however important to stress that EC is not a regular contraceptive method, as already stated in section 4.4:

“EllaOne is for occasional use only. It should in no instance replace a regular contraceptive method. In any case, women should be advised to adopt a regular method of contraception.”

2.3. Clinical Efficacy aspects

2.3.1. Methods – analysis of data submitted

The following studies were submitted by the MAH in support of the variation application.

2.3.1.1.1. HRA2914-515

This post-authorization Phase IV observational study has been undertaken with the objective of assessing safety, tolerability and efficacy in routine conditions of use for EC in postmenarcheal adolescent girls and adult women. Postmenarcheal adolescents or adult women were included in Sweden, France, the United-States and Germany and aged from 13 years old in the United Kingdom. In contrast to previous clinical trials of ella/ellaOne in which women were only eligible for inclusion if they reported a history regular menstrual cycles, no such restrictions were placed on enrolment in this observational study.

As agreed with the Paediatric Committee (PDCO) during the PIP procedure (EMEA-000305-PIP01-08-M02), the sample size of this study was estimated to provide enough safety information on paediatric population exposed to ellaOne. The objective was to obtain complete cases on 350 subjects with at least half (n=175) being adolescent girls (i.e. below 18 years) including 50 minors aged less than 16 years old. Based on an anticipated 30% rate of loss to follow-up, it was planned to enrol 500 subjects overall (250 in each population). The recruitment stopped for each population once 175 unique adolescent subjects (of which 50 minors under 16 years old) had completed the study.

In the initial submission of the type II/021 variation for the change in legal status, the MAH included an interim analysis on the first 228 subjects enrolled. The MAH provided the full study report of study HRA2914-515 in response to the first Request for Supplementary Information. Finally, 579 subjects were included, 279 being under 18 years old (of which 76 were under 16 years old).

Table 4

n (%) subjects	Total	Classification 16*		Classification 18*	
		< 16 years old	≥ 16 years old	< 18 years old	≥ 18 years old
All subjects	**579**	76	502	279	299
ITT population	**579 (100%)**	76 (100%)	502 (100%)	279 (100%)	299 (100%)
mITT population	**464 (80.1%)**	67 (88.2%)	396 (78.9%)	242 (86.7%)	221 (73.9%)
Per Protocol population	**406 (70.1%)**	61 (80.3%)	345 (68.7%)	210 (75.3%)	196 (65.6%)
Safety population	**472 (81.5%)**	64 (84.2%)	408 (81.3%)	239 (85.7%)	233 (77.9%)
Modified safety population**	**471 (81.3%)**	64 (84.2%)	407 (81.1%)	239 (85.7%)	232 (77.6%)

**Age was missing for 1 subject*
***Subject 1705 was excluded from modified safety population because she had inconsistent date of start of treatment cycle and vaginal bleeding.*

The modified Intent-To-Treat (mITT) population was composed of a subset of the ITT population with a known pregnancy status after EC intake, defined as pregnancy status in 'Not pregnant' or 'Pregnant' on the study completion form. The mITT population was the primary population of interest for the efficacy analysis. Demographics analyses were also performed on this population.

The efficacy criterion for evaluation was the pregnancy rate calculated as the number of subjects becoming pregnant after treatment divided by the number of subjects enrolled.

A pregnancy was reported for seven subjects (1.5%) of the 464 subjects included in the mITT population (Table 5): two subjects aged under 18 years old (none under 16 years old) and five subjects aged 18 years or older. One of these pregnancies (term pregnancy with healthy birth at 38 weeks) was considered possibly related to treatment failure according to the investigators and based on menstrual period at the treatment cycle, date of the pregnancy diagnosis and stage of pregnancy at the time of the transvaginal ultrasound. All other pregnancies were not treatment failures as the subjects had a return of menses after treatment intake. The outcome of the pregnancy was elective

abortion for four of them, spontaneous miscarriage for one and unknown for one subject lost to follow-up.

Table 5: Pregnancy rates and relative risk [95%CI] between classes of age – mITT population

	Total (N=464)	Classification 16*			Classification 18*		
		< 16 years old (N=67)	≥ 16 years old (N=396)	RR [95%CI]	< 18 years old (N=242)	≥ 18 years old (N=221)	RR [95%CI]
Pregnancy status							
Not pregnant	**457 (98.5%)**	67 (100%)	389 (98.2%)	1.02 [1.01;1.04]	240 (99.2%)	216 (97.7%)	1.01 [0.99;1.04]
Pregnant	**7 (1.5%)**	0	7 (1.8%)	0.39 [NE ; NE]	2 (0.8%)	5 (2.3%)	0.42 [0.08;2.12]
Pregnancy related to treatment failure							
n	**7**	0	7		2	5	
Yes	**1 (14.3%)**		1 (14.3%)		0	1 (20.0%)	
No	**6 (85.7%)**		6 (85.7%)		2 (100%)	4 (80.0%)	

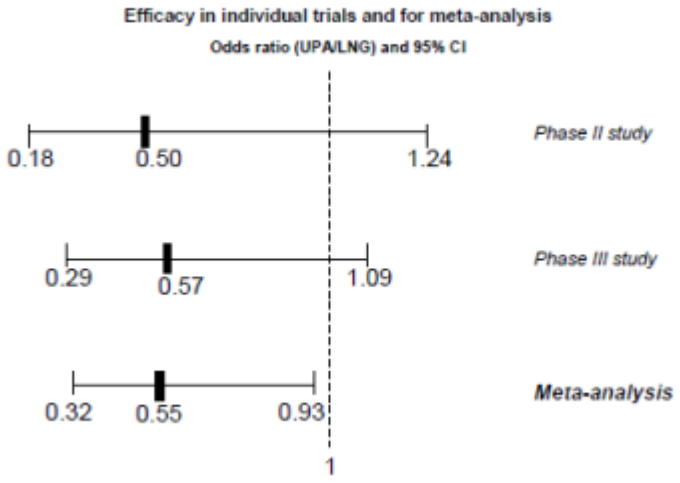
Source: Table 14.3.1.1
No missing data
*Age was missing for 1 subject

The MAH concluded that the results confirm the efficacy profile of ellaOne in routine conditions of use in both postmenarcheal adolescent and adult women.

2.3.1.1.2. Meta-analysis of comparative trials vs. levonorgestrel (HRA2914-541)

In the meta-analysis of the comparative trials versus levonorgestrel (HRA2914-507 and HRA2914-513), the treatment effect was firstly analysed on the overall database (n=3445).

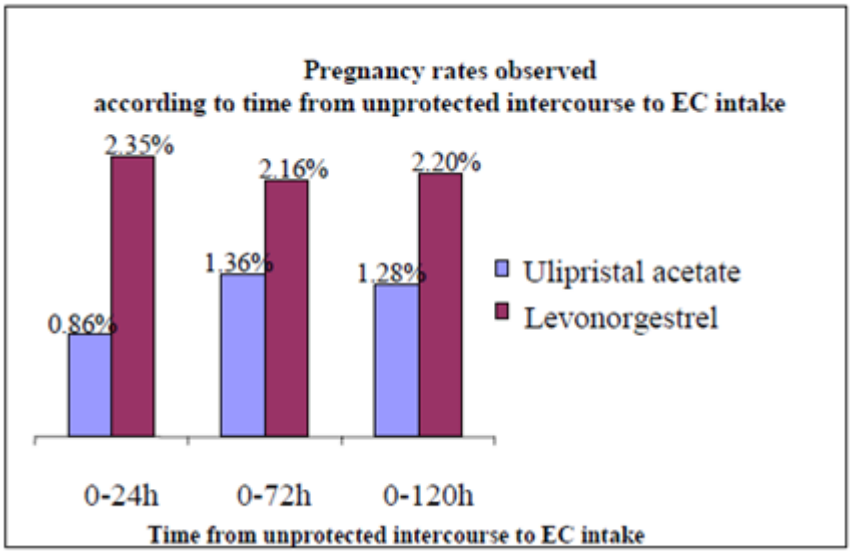
Figure 1: Comparison of risk of pregnancy with ulipristal acetate vs levonorgestrel (OR of pregnancy rates and 95% CI) in individual studies and meta-analysis



Although each comparative study individually showed a trend toward a better efficacy of ulipristal acetate over levonorgestrel (O.R. = 0.50 [0.18-1.24] in phase II study HRA2914-507 and O.R. = 0.57 [0.29-1.09] in phase III study HRA2914-513), statistical superiority was not reached: the upper bounds of the 95% CI were both above the value of 1. When combining data in a meta-analysis, the resulting odds ratio is 0.55 with a 95% CI of 0.32–0.93, therefore the MAH concluded statistical superiority of ulipristal acetate over levonorgestrel.

Observed pregnancy rates were estimated according to different time windows from unprotected intercourse to EC intake: 0-24h, 0-72h and 0-120h (Figure 2). Ulipristal acetate seems to have higher efficacy whatever the time window.

Figure 2: Pregnancy rates (ulipristal acetate vs levonorgestrel) according to time to EC



2.3.2. Discussion and conclusion by the CHMP

2.3.2.1.1. HRA2914-515

The objective of obtaining complete cases on 175 adolescent girls (i.e. below 18 years) including 50 minors aged less than 16 years old was met.
Seven out of 464 subjects (comprising the mITT population), i.e. 1.5%, became pregnant. This observed pregnancy rate is in accordance with the pregnancy rate present in the SmPC of ellaOne, i.e. 1.36%. Two subjects under 18 years of age (but older than 16 years) became pregnant. In the category <18 years old the pregnancy rate was lower than in the category ≥ 18 years old, 0.8% vs. 2.3%, respectively. The CHMP agrees that results in adolescents are consistent with those obtained in adults.

2.3.2.1.2. Meta-analysis of comparative trials vs. levonorgestrel (HRA2914-541)

The results of the HRA2914-507 and HRA2914-513 studies show a lower pregnancy rate after ellaOne intake compared to levonorgestrel in the different time windows. However, statistical superiority was not reached for the individual studies. When combining data in a meta-analysis on efficacy over a period of 0-120h, the MAH concluded statistical superiority of ulipristal acetate over levonorgestrel, but it has to be noted though that levonorgestrel is not registered for the time window 72-120h.

In the SmPC, information was already included in section 5.1 on the efficacy of ulipristal acetate in comparison to levonorgestrel for the time window 0-72 h after unprotected intercourse.

“Results from two independent randomized controlled trials (see Table) showed the efficacy of ulipristal acetate to be non-inferior to that of levonorgestrel in women who presented for emergency contraception between 0 and 72 hours after unprotected intercourse or contraceptive failure. When the data from the two trials were combined via meta-analysis, the risk of pregnancy with ulipristal acetate was significantly reduced compared to levonorgestrel (p=0.046).”

2.4. Clinical Safety aspects

2.4.1. Methods – analysis of data submitted

The MAH submitted the following studies in support of this variation.

2.4.1.1.1. HRA2914-515 - Post-authorization Phase IV observational study

The safety criterion for evaluation was the incidence of adverse events and bleeding patterns. These were analysed during the follow-up period up to two months after ella/ellaOne intake. For subjects who became pregnant, pregnancy follow-up up to outcome and newborns' health status was performed through routine pharmacovigilance procedures for marketed products.

Baseline characteristics

The Safety population included 239 subjects (51%) under 18 years old (with 64 subjects (14%) under 16 years old), and 233 subjects (49%) aged 18 years or older. Overall, subjects were aged from 13 to 46 years old, with a median of 17 years. Data on age are summarised for each age class in Table 6.

Table 6: Age of subjects – Safety Population

	Total (N=472)	Classification 16		Classification 18	
		< 16 years old (N=64)	≥ 16 years old (N=408)	< 18 years old (N=239)	≥ 18 years old (N=233)
Age (years)					
n	**472**	64	408	239	233
Mean (SD)	**19.5 (5.4)**	14.6 (0.6)	20.3 (5.4)	16.0 (1.0)	23.1 (5.6)
Median	**17.0**	15.0	18.0	16.0	21.0
Min. ; Max.	**13.0 ; 46.0**	13.0 ; 15.0	16.0 ; 46.0	13.0 ; 17.0	18.0 ; 46.0
Age in classes					
n	**472**	64	408	239	233
< 16 years	**64 (13.6%)**	64 (100%)	0	64 (26.8%)	0
≥ 16 - < 18 years	**175 (37.1%)**	0	175 (42.9%)	175 (73.2%)	0
≥ 18 - ≤ 35 years	**222 (47.0%)**	0	222 (54.4%)	0	222 (95.3%)
>35 years	**11 (2.3%)**	0	11 (2.7%)	0	11 (4.7%)

Mean age was higher in the United States where there was no subject under 16 years old and only 22 subjects under 18 years old and in Germany where the majority of subjects (53 out of 92) were aged 18 years or older. In France, 23 out of the 45 patients included in the Safety population were under 18 years old (including 10 under 16 years old). In Sweden and in the United Kingdom, the majority of subjects was under 18 years old: 63 (including 19 under 16 years old) out of 92 and 92 (including 21 under 16 years old) out of 128, respectively (Table 7).

Table 7: Age of subjects by country – Safety Population

Age (years)	France	Germany	Sweden	United Kingdom	United States
n	45	92	92	128	115
Mean (SD)	18.9 (6.0)	21.0 (6.6)	16.9 (1.9)	17.5 (3.2)	22.9 (5.7)
Median	17.0	19.0	17.0	17.0	22.0
Min. ; Max.	14.0 ; 46.0	14.0 ; 45.0	13.0 ; 22.0	14.0 ; 33.0	16.0 ; 40.0

Overall, subjects had a weight between 34 and 144 kg, with a mean (±SD) of 63.2 (±15.3) kg. Among the subjects under 18 years old, 10% had a BMI <18 kg/m² and 76% had a BMI between 18 kg/m² and 25 kg/m². BMI over 25 kg/m² was more frequent in subjects aged 18 years or older: 42% of the subjects compared to 14% of the subjects under 18 years old (Table 8).

Table 8: Anthropometric data overall – Safety Population

		Classification 16		Classification 18	
	Total (N=472)	< 16 years old (N=64)	≥ 16 years old (N=408)	< 18 years old (N=239)	≥ 18 years old (N=233)
Weight (kg)					
n	**470**	64	406	239	231
Mean (SD)	**63.24 (15.29)**	55.05 (8.89)	64.53 (15.69)	57.94 (10.34)	68.72 (17.51)
Median	**60.00**	53.00	60.30	56.30	63.70
Min. ; Max.	**34.0 ; 144.0**	34.0 ; 90.0	40.0 ; 144.0	34.0 ; 100.0	40.0 ; 144.0
Missing data	**2**	0	2	0	2
Height (m)					
n	**471**	64	407	238	233
Mean (SD)	**1.64 (0.07)**	1.63 (0.05)	1.65 (0.07)	1.64 (0.06)	1.65 (0.07)
Median	**1.65**	1.63	1.65	1.64	1.65
Min. ; Max.	**1.5 ; 1.8**	1.5 ; 1.8	1.5 ; 1.8	1.5 ; 1.8	1.5 ; 1.8
Missing data	**1**	0	1	1	0
BMI (kg/m²)					
n	**469**	64	405	238	231
Mean (SD)	**23.39 (5.40)**	20.74 (3.19)	23.81 (5.56)	21.56 (3.60)	25.27 (6.24)
Median	**22.09**	19.97	22.49	20.95	23.42
Min. ; Max.	**14.2 ; 49.1**	14.2 ; 31.1	15.2 ; 49.1	14.2 ; 37.9	16.5 ; 49.1
Missing data	**3**	0	3	1	2
in classes					
< 18 kg/m²	**36 (7.7%)**	9 (14.1%)	27 (6.7%)	24 (10.1%)	12 (5.2%)
≥ 18 - < 25 kg/m²	**303 (64.6%)**	49 (76.6%)	254 (62.7%)	181 (76.1%)	122 (52.8%)
≥ 25 - < 30 kg/m²	**81 (17.3%)**	5 (7.8%)	76 (18.8%)	25 (10.5%)	56 (24.2%)
≥ 30 - < 35 kg/m²	**27 (5.8%)**	1 (1.6%)	26 (6.4%)	5 (2.1%)	22 (9.5%)
≥ 35 kg/m²	**22 (4.7%)**	0	22 (5.4%)	3 (1.3%)	19 (8.2%)
Missing data	**3**	0	3	1	2

The median duration of menstrual cycle was 28 days for all age classes. It was less than 24 days for 10 subjects, including two subjects under 18 years old, and longer than 45 days for four subjects, including three under 18 years old.

Overall, 145 subjects (31%) had irregular cycles within the last year. Irregular cycles were more frequent in younger subjects: 36% of the subjects under 18 years old compared to 26% of the subjects aged 18 years and older.

Spotting within the last year was reported in 9% of the subjects, less often among subjects under 18 years old compared to subjects aged 18 years or older (7% versus 10%). Metrorrhagia within the last year was reported for 22 subjects under 18 years old (9% of this age group), including three subjects under 16 years old, and 18 subjects aged 18 years or older (8% of this age group). Amenorrhea within the last year was reported for 38 subjects (8%), more often among subjects under 18 years old (11%).

Table 9: Average menstrual cycle length and menstrual history – Safety Population

	Total (N=472)	Classification 16		Classification 18	
		< 16 years old (N=64)	≥ 16years old (N=408)	< 18 years old (N=239)	≥ 18 years old (N=233)
Average menstrual cycle length (days)					
n	**423**	61	362	218	205
Mean (SD)	**29.12 (5.47)**	29.16 (2.87)	29.11 (5.80)	29.83 (6.77)	28.37 (3.47)
Median	**28.00**	28.00	28.00	28.00	28.00
Min. ; Max.	**17.0 ; 90.0**	24.0 ; 44.0	17.0 ; 90.0	21.0 ; 90.0	17.0 ; 60.0
Missing data	**49**	3	46	21	28
in classes:					
< 24 days	**10 (2.4%)**	0	10 (2.8%)	2 (0.9%)	8 (3.9%)
≥ 24 - ≤ 35 days	**400 (94.6%)**	60 (98.4%)	340 (93.9%)	207 (95.0%)	193 (94.1%)
> 35 - ≤ 45 days	**9 (2.1%)**	1 (1.6%)	8 (2.2%)	6 (2.8%)	3 (1.5%)
> 45 days	**4 (0.9%)**	0	4 (1.1%)	3 (1.4%)	1 (0.5%)
Missing data	**49**	3	46	21	28
History of irregular cycles within the last year	**145 (30.7%)**	21 (32.8%)	124 (30.4%)	85 (35.6%)	60 (25.8%)
History of spotting within the last year	**40 (8.5%)**	5 (7.8%)	35 (8.6%)	16 (6.7%)	24 (10.3%)
History of metrorrhagia within the last year	**40 (8.5%)**	3 (4.7%)	37 (9.1%)	22 (9.2%)	18 (7.8%)
Missing data	**1**	0	1	0	1
History of amenorrhea within the last year	**38 (8.1%)**	8 (12.5%)	30 (7.4%)	25 (10.5%)	13 (5.6%)
Missing data	**2**	0	2	0	2

The time between the UPI motivating EC and ella/ellaOne intake ranged from less than 1 hour to 298 hours (12 days), with a median of 43 hours. Nine subjects took the treatment more than 120 hours after the UPI: five under 18 years old (and over 16 years old) and four aged 18 years or older. Most subjects (51%) took the treatment between 24 and 72 hours after the UPI. Among the subjects under 18 years old, 17% took the treatment between 72 and 96 hours after the UPI (compared to 6% of the subjects aged 18 years or older) and 26% took the treatment within 24 hours after the UPI (compared to 31% of the subjects aged 18 years or older).

Table 10: Sexual intercourse motivating EC and ella / ellaOne intake – Safety Population

	Total (N=472)	Classification 16		Classification 18	
		< 16 years old (N=64)	≥ 16 years old (N=408)	< 18 years old (N=239)	≥ 18 years old (N=233)
Time between ella®/ellaOne® intake and UPI motivating EC (hours)					
n	**472**	64	408	239	233
Mean (SD)	**49.3 (35.4)**	50.8 (32.6)	49.1 (35.9)	53.8 (35.5)	44.7 (34.8)
Median	**43.0**	47.3	42.4	47.7	37.1
Min. ; Max.	**0.0 ; 297.6**	1.0 ; 120.0	0.0 ; 297.6	1.0 ; 236.5	0.0 ; 297.6
in classes					
< 12 hours	**30 (6.4%)**	2 (3.1%)	28 (6.9%)	11 (4.6%)	19 (8.2%)
12 to 24 hours	**106 (22.5%)**	19 (29.7%)	87 (21.3%)	52 (21.8%)	54 (23.2%)
>24 to 48 hours	**125 (26.5%)**	12 (18.8%)	113 (27.7%)	57 (23.8%)	68 (29.2%)
>48 to 72 hours	**115 (24.4%)**	14 (21.9%)	101 (24.8%)	53 (22.2%)	62 (26.6%)
>72 to 96 hours	**55 (11.7%)**	10 (15.6%)	45 (11.0%)	41 (17.2%)	14 (6.0%)
>96 to 120 hours	**32 (6.8%)**	7 (10.9%)	25 (6.1%)	20 (8.4%)	12 (5.2%)
>120 hours	**9 (1.9%)**	0	9 (2.2%)	5 (2.1%)	4 (1.7%)

Adverse events

A total of 350 treatment-emergent AEs (TEAEs) were reported in 148 subjects (31%), mainly of mild or moderate intensity (Table 11). Only 11 TEAEs (3%) were considered of severe intensity, mostly headache. One TEAE was serious.
The serious adverse event occurred in an adolescent subject. The subject was hospitalized 12 days after ellaOne intake for suspected urinary tract infection, abdominal pain and vomiting, she was released after 2 days of IV fluids and paracetamol, and completely recovered after 5 days. The patient was diagnosed with a possible viral illness. The investigator assessed the causal relationship with study drug as unlikely.

Table 11: Summary of treatment emergent adverse events – Safety Population

	Total (N=472)		< 16 years old (N=64)		≥ 16 years old (N=408)		< 18 years old (N=239)		≥ 18 years old (N=233)	
	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects
Any TEAE	350	148 (31.4%)	47	19 (29.7%)	303	129 (31.6%)	171	68 (28.5%)	179	80 (34.3%)
TEAE potentially related to study treatment*	107	57 (12.1%)	8	6 (9.4%)	99	51 (12.5%)	39	23 (9.6%)	68	34 (14.6%)
Serious TEAE	1	1 (0.2%)	0	0	1	1 (0.2%)	1	1 (0.4%)	0	0
Serious TEAE potentially related to study treatment*	0	0	0	0	0	0	0	0	0	0

Source: Table 14.2.1.2, Table 14.2.1.9, Table 14.2.1.12 and Table 14.2.1.13.
* Relationship noted as "Certain", "Possible" or "Probable".

The most frequently reported TEAEs were headache (51 subjects, 11%), nausea (30 subjects, 6%) and abdominal pain (16 subjects, 3%), with similar incidence in the different age classes. Upper abdominal pain was reported for 15 subjects (3%), more frequently in subjects under 16 years old (8% compared to 3% of the subjects aged 16 years or older) with a relative risk [95%CI] of 3.3 [1.2;9.5]. About a third of these TEAEs were reported within 5 days after treatment intake.

A total of 107 TEAEs reported in 57 subjects (12%) were considered as related to the study treatment (certainly, probably or possibly), mainly nausea (22 subjects, 5%), headache (14 subjects, 3%), abdominal pain (10 subjects, 2%) and dizziness (six subjects, 1%).

Table 12: TEAEs potentially related to study treatment presented by SOC and PT – Safety Population

	Total (N=472)		Classification 16				Classification 18			
			< 16 years old (N=64)		≥ 16 years old (N=408)		< 18 years old (N=239)		≥ 18 years old (N=233)	
	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects
Any TEAE potentially related to ella®/ellaOne®*	107	57 (12.1%)	8	6 (9.4%)	99	51 (12.5%)	39	23 (9.6%)	68	34 (14.6%)
Gastrointestinal disorders	46	38 (8.1%)	2	2 (3.1%)	44	36 (8.8%)	15	11 (4.6%)	31	27 (11.6%)
Nausea	22	22 (4.7%)	0	0	22	22 (5.4%)	8	8 (3.3%)	14	14 (6.0%)
Abdominal pain	10	10 (2.1%)	0	0	10	10 (2.5%)	3	3 (1.3%)	7	7 (3.0%)
Abdominal pain lower	3	3 (0.6%)	0	0	3	3 (0.7%)	0	0	3	3 (1.3%)
Abdominal pain upper	4	3 (0.6%)	1	1 (1.6%)	3	2 (0.5%)	1	1 (0.4%)	3	2 (0.9%)
Diarrhoea	2	2 (0.4%)	1	1 (1.6%)	1	1 (0.2%)	1	1 (0.4%)	1	1 (0.4%)
Vomiting	2	2 (0.4%)	0	0	2	2 (0.5%)	0	0	2	2 (0.9%)
Abdominal distension	1	1 (0.2%)	0	0	1	1 (0.2%)	1	1 (0.4%)	0	0
Dyspepsia	1	1 (0.2%)	0	0	1	1 (0.2%)	1	1 (0.4%)	0	0
Flatulence	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Nervous system disorders	26	22 (4.7%)	3	3 (4.7%)	23	19 (4.7%)	13	12 (5.0%)	13	10 (4.3%)
Headache	15	14 (3.0%)	2	2 (3.1%)	13	12 (2.9%)	9	9 (3.8%)	6	5 (2.1%)
Dizziness	6	6 (1.3%)	1	1 (1.6%)	5	5 (1.2%)	3	3 (1.3%)	3	3 (1.3%)
Migraine	4	3 (0.6%)	0	0	4	3 (0.7%)	1	1 (0.4%)	3	2 (0.9%)
Somnolence	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Reproductive system and breast disorders	17	12 (2.5%)	1	1 (1.6%)	16	11 (2.7%)	7	5 (2.1%)	10	7 (3.0%)
Breast tenderness	5	4 (0.8%)	0	0	5	4 (1.0%)	1	1 (0.4%)	4	3 (1.3%)
Dysmenorrhoea	4	4 (0.8%)	1	1 (1.6%)	3	3 (0.7%)	3	3 (1.3%)	1	1 (0.4%)
Breast pain	2	2 (0.4%)	0	0	2	2 (0.5%)	1	1 (0.4%)	1	1 (0.4%)
Pelvic discomfort	2	2 (0.4%)	0	0	2	2 (0.5%)	1	1 (0.4%)	1	1 (0.4%)
Menorrhagia	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Menstrual discomfort	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Pelvic pain	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Vaginal discharge	1	1 (0.2%)	0	0	1	1 (0.2%)	1	1 (0.4%)	0	0

	Total (N=472)		Classification 16				Classification 18			
			< 16 years old (N=64)		≥ 16 years old (N=408)		< 18 years old (N=239)		≥ 18 years old (N=233)	
	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects
General disorders and administration site conditions	6	4 (0.8%)	1	1 (1.6%)	5	3 (0.7%)	3	2 (0.8%)	3	2 (0.9%)
Fatigue	2	2 (0.4%)	0	0	2	2 (0.5%)	0	0	2	2 (0.9%)
Pain	2	2 (0.4%)	1	1 (1.6%)	1	1 (0.2%)	2	2 (0.8%)	0	0
Malaise	1	1 (0.2%)	0	0	1	1 (0.2%)	1	1 (0.4%)	0	0
Pyrexia	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Musculoskeletal and connective tissue disorders	4	4 (0.8%)	1	1 (1.6%)	3	3 (0.7%)	1	1 (0.4%)	3	3 (1.3%)
Muscle spasms	2	2 (0.4%)	0	0	2	2 (0.5%)	0	0	2	2 (0.9%)
Back pain	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Groin pain	1	1 (0.2%)	1	1 (1.6%)	0	0	1	1 (0.4%)	0	0
Psychiatric disorders	3	3 (0.6%)	0	0	3	3 (0.7%)	0	0	3	3 (1.3%)
Depression	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Loss of libido	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Mood swings	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Skin and subcutaneous tissue disorders	3	3 (0.6%)	0	0	3	3 (0.7%)	0	0	3	3 (1.3%)
Acne	2	2 (0.4%)	0	0	2	2 (0.5%)	0	0	2	2 (0.9%)
Pruritus	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Metabolism and nutrition disorders	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Food craving	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Vascular disorders	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)
Hot flush	1	1 (0.2%)	0	0	1	1 (0.2%)	0	0	1	1 (0.4%)

Source: Table 14.2.1.9.
*Potentially related: relationship noted as "Certain", "Possible" or "Probable".

There was no statistically significant difference between subjects under 18 years old and subjects aged 18 years and older regarding the intensity (p=0.302) and time of occurrence of TEAEs (p=0.106). TEAEs related to treatment were more frequently reported in subjects aged 18 years or older (38% of the subjects compared to 23% of the subjects under 18 years old, p=0.003). Similar results were observed when comparing subjects under 16 years old and subjects aged 16 years and older.

Adverse event of interest – vaginal bleeding

Dysmenorrhea (defined as painful menstrual period and/or premenstrual symptoms) was reported as an adverse event in nine subjects (2%), five under 18 years old (including one under 16 years old) and four aged 18 years or older. None of these subjects had reported previous history of dysmenorrhea.

Menorrhagia (heavy or prolonged (>7 days) menstrual period) was reported in 140 subjects (30%) overall, more frequently among subjects aged 18 years or older: 37% compared to 23% of the subjects under 18 years old.

Metrorrhagia (bleeding occurring outside of menstrual period) was reported in 99 subjects (21%) during the study. The first metrorrhagia occurred from 0 to 68 days after ella/ellaOne intake, with a median time of 10 days overall: 13 days for subjects under 18 years old and 5.5 days for subjects aged 18 years or older. Overall, 62 subjects (13%) experienced metrorrhagia during the treatment cycle from the time of intake of study treatment, more frequently when there was a previous history of spotting: 23% compared to 12% of the subjects without such medical history. Metrorrhagia lasted for a median of 3 days and consisted of spotting in 82% of the cases. Heavy metrorrhagia was reported for three subjects (one under 16 years old, one 16-17 years old and one aged 18 years or older) and lasted between 1 and 4 days. There was no statistically significant difference between age classes in terms of incidence, duration and volume of metrorrhagia occurring during the treatment cycle from intake of study treatment. Similar results were observed for metrorrhagia occurring during the first post-treatment cycle.

Table 13: Incidence and relative risk [95% CI] between age classes for events of interest – Safety Population

	Total (N=472)	Classification 16			Classification 18		
		< 16 years old (N=64)	≥ 16 years old (N=408)	RR [95%CI]	< 18 years old (N=239)	≥ 18 years old (N=233)	RR [95%CI]
Dysmenorrhea	9 (1.9%)	1 (1.6%)	8 (2.0%)	1.13 [0.14;8.85]	5 (2.1%)	4 (1.7%)	1.19 [0.32;4.38]
Menorraghia	140 (29.7%)	14 (21.9%)	126 (30.9%)	0.73 [0.45;1.19]	54 (22.6%)	86 (36.9%)	0.61 [0.46;0.82]
Metrorrhagia	99 (21.0%)	13 (20.3%)	86 (21.1%)	0.99 [0.59;1.67]	51 (21.3%)	48 (20.6%)	1.04 [0.73;1.47]
Change of length of treatment or post-treatment cycle >7 days*	174 (45.2%)	28 (50.9%)	146 (44.2%)	1.17 [0.88;1.55]	104 (52.5%)	70 (37.4%)	1.40 [1.11;1.76]
Change of length of treatment cycle > 7 days*	142 (37.0%)	23 (42.6%)	119 (36.1%)	1.18 [0.84;1.66]	84 (42.6%)	58 (31.0%)	1.36 [1.04;1.78]
Change of length of post-treatment cycle >7 days**	52 (26.0%)	5 (17.9%)	47 (27.3%)	0.71 [0.31;1.63]	28 (30.4%)	24 (22.2%)	1.37 [0.85;2.18]

Source: Table 14.2.1.1

**Percentages are calculated on the number of subjects with available data on average cycle length and length of treatment cycle*

***Percentages are calculated on the number of subjects with available data on average cycle length and length of first post treatment cycle*

Considering the expected small incidence of events, relative risk was corrected by adding 0.5 to the number of subjects presenting the event in each class (see Section 9.7.1.1).

Menstrual periods: Overall, 436 subjects (93%) had a menstrual period (at least once) after ella/ellaOne intake during the follow-up period of the study, lasting for a median of 5 days, whatever the age class (<16 and ≥16 years old; <18 and ≥18 years old). Regular menstrual bleeding was reported for 72% of the subjects, more frequently among younger subjects and heavy menstrual bleeding for 22% of the subjects, more frequently among subjects aged 18 years or older. Data on the second menstrual period post-treatment were available for 331 subjects and showed similar results to those reported for the first menstrual period post-treatment.

Among the 37 subjects who had a history of amenorrhea, 35 (95%) had a first menstrual period after ella/ellaOne intake and 67% had a second menstrual period post-treatment during the follow-up period compared to 93% and 73%, respectively, of those without a history of amenorrhea.

The MAH was requested to provide more information on the 7% of subjects that did not have a menstrual period after ellaOne intake during the follow-up period of study HRA2914-515.

The MAH provided the following information in answer to that request.

This prospective, post-marketing, observational and multicenter open label study was performed in routine conditions of use of emergency contraception (EC) meaning that all-comers were eligible for enrollment, including women with irregular cycles, history of amenorrhea, and current users of hormonal contraception. All women presenting at a participating site and requesting EC who received ellaOne were eligible for the study. Since this study was observational, the follow-up information after inclusion was gathered according to routine practice at any given site, either through a return to clinic visit or through a telephone call at variable times after intake.

Overall, 436/472 subjects (93%) reported a return of menses after ellaOne intake during the study. This percentage was similar for subjects under 18 years old and subjects aged 18 years or older, and slightly numerically higher for subjects under 16 years old (95%).

Table 14: Description of first menstrual period after treatment - Safety Population

		Classification 16		Classification 18	
First menses after ellaOne intake	**Total (N=472)**	**< 16 years old (N=64)**	**≥ 16 years old (N=408)**	**< 18 years old (N=239)**	**≥ 18 years old (N=233)**
Subject with menses after ellaOne intake	**436 (92.8%)**	61 (95.3%)	375 (92.4%)	222 (92.9%)	214 (92.6%)

The different clinical scenarios for all 36 subjects for whom information is available on menses after ellaOne intake are summarized in Table 15. Individual data were also provided. In 17 cases, no or only partial information is available due to loss to follow-up. Of the remaining 19 cases, extenuating clinical circumstances were identified in many cases: irregular cycles (n=7) and/or episodes of amenorrhea (n=2) in the past year, or use of hormonal methods of ongoing contraception concomitantly or immediately after ellaOne intake (n=12). In 3 cases (0.6% of the study population), no presumably extenuating circumstances were identified in available clinical data.
Eleven subjects (2.3%) had no return of menses after ≥ 60 days of follow-up, of whom 8 had a plausible clinical reason; seven of them (1.5%) had no return of menses after ≥ 90 days (amenorrhea), and all had a plausible clinical reason (use of hormonal contraception or previous history of irregular cycles). By way of comparison, in the phase III clinical trials (from which subjects with irregular cycles or recent amenorrhea were excluded), amenorrhea of more than 60 days without plausible clinical explanation was reported in 0.4% (8/2488) subjects.

Table 15: Clinical circumstances for the all subjects with no return of menses at the end of the study, grouped by most probable clinical reason

Specific clinical situations	**Tot N of subjects**	**Irregular cycles in the past year**	**Amenorrhea in the past year**	**N with a f/u >90 days (amenorrhea)**
Hormonal contraception quick started after EC or regular contraception started 1-3 weeks after EC	9	5	1	2*
Regular oral contraception at the time of EC	3	0	1	3**
Completed the study without return of menses	7	2	0	0
Lost to follow-up (LFU), with f/u duration available	7	5	0	2†
LFU with no information	10	4	1	-
Total	**36**	**16**	**3**	**7**

*progestin-only contraception (Implanon and Depot Provera)
**Cerazette in 2 cases and Yaz in one case
† both cases had declared irregular cycles in the past year

In summary, amenorrhea with no identified clinical etiology was a rare event in this real-life study, with an incidence similar to that reported in Phase III trials. In subjects who did not report menses after ellaOne intake, concomitant hormonal treatment (mainly progestin-only and long-acting methods which are usually associated with absence of menses) is the most likely explanation, with irregular cycles or amenorrhea at baseline also possibly having played a role. The subject's age did not seem to impact the risk of not having menses after treatment.

Menstrual cycles: Compared to the median average menstrual cycle length of 28 days reported at inclusion, the treatment cycle was generally longer with a median of 31 days. The median change in length of menstrual cycle was 6 days in subjects under 18 years old and 4 days in subjects aged 18 years or older. Post-treatment menstrual cycle had a median duration of 28 days, comparable to average menstrual cycle. Changes of more than 7 days in length of treatment cycle or post-treatment cycle were significantly more often reported in subjects under 18 years old: in 53% compared to 37% of the subjects aged 18 years or older (relative risk [95%CI] of 1.4 [1.1;1.8]).

For subjects with a history of irregular cycle (n=145), the median duration of treatment cycle was 31 days and the median change in cycle length was 7 days (compared to 30 days and 4 days, respectively, in subjects without such medical history). The first post-treatment cycle length was similar for subjects with and without history of irregular cycles.

Twenty seven (27) subjects reported a complete second menstrual cycle post-treatment during the study: 11 subjects under 18 years old (including five under 16 years old) and 16 subjects aged 18 years or older. The median duration of this second post-treatment cycle was 28 days and the median change in cycle length compared to average length at enrolment was 2 days.

Sexual intercourse after treatment intake: Between treatment intake and first menstrual period, 44% of the subjects had at least one sexual intercourse, more often among subjects aged 18 years or older (49%) and less often among subjects under 18 years old (39%), and the difference between age classes was close to statistically significance (p=0.056). Among these subjects, 28% had at least one act of unprotected intercourse, with no significant difference between age classes.

2.4.1.1.2. HRA2914-555 – Pooled phase III safety analysis by age groups, race and region

Study HRA2914-555 performed an additional analysis by age, race and region. The type and frequency of the most common adverse events did not differ between the age categories (<18, 18-25, >25-35, >35). No differences were observed in the type and frequency of AE between women of different races in the Phase III studies. Furthermore, the type and frequency of AE did not differ between geographic regions (Europe or USA).

2.4.1.1.3. HRA2914-558 - Analysis of intermenstrual bleeding episodes in studies HRA2914-509 and HRA2914-513

The aim of this study was to calculate descriptive statistics on variables related to intermenstrual bleedings on 2637 women for the Phase III trials. The variables of interest were:
- Number of women with intermenstrual bleedings
- Time to bleeding
- Duration of bleeding
- Intensity of bleeding

These statistics were performed for:
- All women,
- Separating pregnant and non-pregnant women,

• Among pregnant women, separating miscarriages from “other pregnancy”.

The MAH concluded that compared to all women for which metrorrhagia was reported in 8.5-8.7%, in both studies, pregnant women reported a metrorrhagia episode in 27.6% of cases in study HRA2914-509 and in 40% of women in study HRA2914-513 (8 subjects each). Women who had a spontaneous miscarriage reported metrorrhagia in 1 case (25%) in HRA2914-509 and 2 cases (33%) in HRA2914-513. Only one heavy bleeding episode was reported in a woman who had a miscarriage. When metrorrhagia was reported, it lasted a mean of 2 days and occurred a mean of 9.5 and 6.1 days after treatment in all pregnant subjects, and a mean of 10 and 15 days after treatment in subjects who then had a miscarriage in studies HRA2914-509 and HRA2914-513.

2.4.1.1.4. Pregnancy data

- **Method for ruling out pregnancy in clinical practice**

During the assessment of the variation, the MAH was requested to provide information on how HCPs rule out pregnancy before they prescribe ellaOne in practice.

The MAH answered that when prescribing emergency contraception (EC), regardless of the method, HCPs rule out pregnancy via clinical questioning. No medical examination is performed (UK FSRH Guidance on emergency contraception, 2012). Clinical questioning focuses on two topics: the date of the episode of unprotected intercourse and the date of the woman’s last menstrual period.

The results of study HRA2914-552 (conducted in the context of MEA 008) confirm that this is indeed the approach used by HCPs when prescribing ellaOne. In this survey, HCPs participated in face-to-face interviews using an open-ended questioning approach. The interviews focused on their prescribing practices.
When questioned about what they ask before prescribing ellaOne, all 90 HCPs interviewed spontaneously specified the date of the unprotected intercourse, and 87 out of 90 mentioned asking about patients’ last menstrual period.

The two most commonly-asked questions are:
1. When did the unprotected intercourse take place? to verify that EC is indicated, and that a pregnancy may not have started from intercourse several weeks earlier in the cycle.
2. When did you have your last menstrual period? to verify that the woman did not become pregnant in her previous cycle.

In summary, HCPs rely on the information provided by a woman about her last menstrual period:
1. If her menstrual period is not late, it is concluded that she is not pregnant.
2. If her menstrual period is late, a pregnancy test could provide additional information at this point in time. This is when test should be performed.

The proposed product information for ellaOne addresses the topic of ruling out pregnancy in a non-prescription setting using the same approach.

- **Collection of pregnancy data in a “non-prescription setting”**

This concern was raised by the CHMP during the assessment of the variation because collecting pregnancy data in a “non-prescription setting” might be more challenging. Previous experience with a change in prescription status is available with another EC product that first was delivered under “prescription only” before being available “non-prescription”. The MAH was requested to provide comparative data to show how the reporting of undesirable effects, including pregnancy exposure, was affected by the switch to “non-prescription” status.

The MAH provided some comparative data with levonorgestrel (LNG) in their answer.

The pregnancy reporting data for LNG show a similar low level of reporting both for prior and post its switch to non-prescription status.
For ellaOne, a higher reporting rate of pregnancy has been observed compared to LNG, which may have resulted from specific efforts made by the MAH to increase reporting. This difference exists regardless of the time since launch for LNG (total period or first four years only) considered for the comparison.

After reclassification, the MAH commits to continue the promotion of pregnancy reporting especially to healthcare professionals who see pregnant women.
The MAH also proposes to include the address of the pregnancy registry website in the product information (Summary of Product Characteristics and Package Leaflet) of ellaOne in order to emphasize the importance of the pregnancy reporting.

In conclusion the MAH does not foresee that a change of legal status to non-prescription would lead to a reduction in the reporting of pregnancy.

2.4.2. Discussion by the CHMP

2.4.2.1.1. HRA2914-515 (post-authorization Phase IV observational study)

The CHMP agrees with the fact that the causal relationship for the serious adverse event “possible viral illness” with ellaOne is unlikely.

There were no clinically relevant differences between subjects under 18 years old and subjects aged 18 years and older in the occurrence of TEAEs. The incidence of dysmenorrhea and metrorrhagia was similar in women below and over 18 years old. Menorrhagia (heavy or prolonged (>7 days) menstrual period) was higher in the group above 18 years old, compared to the women below 18 years old.

The MAH was requested by the CHMP to provide more information on the 7% of subjects that did not have a menstrual period after ellaOne intake during the follow-up period of the study.
In answer to that request, the MAH provided extensive information on the 7% of subjects that did not have a menstrual period after ellaOne intake during the follow-up period of study HRA2914-515. In contrast to the clinical studies for registration, in study HRA2914-515, the subjects included did not have to have regular cycles before ellaOne intake. Further, in trial HRA2914-515 women could also start with concomitant intake of hormonal contraceptives next to ellaOne. Hormonal treatment with progesterone-only contraception methods can lead to amenorrhea.
The CHMP endorsed the conclusion of the MAH that ‘in subjects who did not report menses after ellaOne intake, concomitant hormonal treatment is the most likely explanation, with irregular cycles or amenorrhea at baseline also possibly having played a role’.
The following information is currently present in the SmPC “In approximately 7% of the women, menstrual periods occurred more than 7 days earlier than expected. In 18.5% of the women a delay of more than 7 days occurred, and in 4% the delay was greater than 20 days”. This information is adequate.

Changes of more than 7 days in length of treatment cycle or post-treatment cycle were more reported in subjects under 18 years old. However, it should be noted that in the baseline characteristics the history of irregular cycles within the last year was also more reported for women below 18 years old (35.6%) compared to above 18 years old (25.8%). Further, women with a history of irregular cycles had a larger median change in cycle length of 7 days compared to women without such a history, who

had a median change of 4 days. The higher percentage of 'changes of more than 7 days in length of treatment cycle or post-treatment cycle' in the group below 18 years is likely explained by the higher incidence of irregular cycles at baseline compared to the group above 18 years old.

Overall, the results show that the safety profile for ellaOne is similar for adolescent girls (<18 years) compared to women above 18 years.

2.4.2.1.2. HRA2914-555 (pooled phase III safety analysis by age groups, race and region)

This study shows that the type and frequency of the most common adverse events does not differ between the age categories (<18, 18-25, >25-35, >35), the race and the geographic region.

2.4.2.1.3. HRA2914-558 - Analysis of intermenstrual bleeding episodes in studies HRA2914-509 and HRA2914-513

This study analyses all intermenstrual bleeding data of the Phase III trials HRA2914-509 and HRA2914-513. The higher percentage of metrorrhagia observed in pregnant women compared to non-pregnant women was expected.

2.4.2.1.4. Pregnancy data

The MAH was asked how HCPs rule out pregnancy before they prescribe ellaOne in practice.
The MAH has asked 90 HCPs in study HRA2914-552 how they excluded pregnancy. The two most commonly-asked questions were: 1. When did the unprotected intercourse take place? 2. When did you have your last menstrual period? A pregnancy test is frequently not useful, because if the pregnancy test is performed too early it will give a false negative result. It is agreed with the MAH that in a non-prescription setting the two questions posed by HCPs to rule out pregnancy, may be asked by pharmacists before providing ellaOne. This information on how to rule out pregnancy is also present in the patient information leaflet.

The MAH was also requested to provide comparative data to show how the reporting of undesirable effects, including pregnancy exposure, was affected by the switch to "non-prescription" status for Norlevo. As the reporting of undesirable effects with Norlevo is limited, the CHMP has accepted that the MAH has focused on the reporting of pregnancies after exposure with ellaOne. Exposure during pregnancy is considered the most important, as there are no concerns regarding other adverse events of ellaOne. Overall, the data of Norlevo show that the change in legal status from "prescription" to "non-prescription" resulted in a similar percentage of pregnancy reporting. These data are reassuring. In addition, the MAH shows that for ellaOne the estimated percentage of pregnancies that are reported are higher than for Norlevo, also when looked at the reporting for both products during the first four years of marketing. For this calculation the numbers of expected pregnancies were calculated with a pregnancy rate of 2.2% for levonorgestrel and 1.3% for ellaOne. These presumed pregnancy rates used for the calculation are acceptable, and are present in the SmPC of ellaOne. The total number of exposed pregnancies is low and therefore the MAH was requested to provide additional pregnancy data. These data are discussed in section 2.5 (third criteria) of this report.

2.4.3. Conclusion by the CHMP

Overall, safety data are available for a large database of exposed women. The adverse event profile of ellaOne is well characterized and adverse reactions reported during the development program and post-marketing phase were for the most part mild to moderate in severity. The most frequently reported adverse reactions were headache, nausea and abdominal pain. Furthermore additional data

is now available for use in adolescents and repeat use of the 30 mg dose which unveiled no unexpected events.

Currently, 3 million women have been treated. Since the initial MA, no new safety concerns were recognized for ellaOne. Further, no new relevant safety findings negatively impacting the benefit-risk ratio of ellaOne have been identified.

In addition, the MAH has taken additional measures to continue increasing the awareness, and underlying the importance of the pregnancy registry, therefore it is not expected that the percentage of pregnancies that is reported will decrease due to a change to a non-prescription status. Thus, the CHMP is of the opinion that the pregnancy registry could also function in a non-prescription setting.

In conclusion, based on a large database collected in a variety of regions and ethnic groups representative of Western populations, no safety signal has been observed since initial MA of ulipristal acetate 30 mg for EC, and extensive post-approval information confirms the safety features defined during clinical development.

The CHMP agrees that no safety signal has been observed since initial MA of ulipristal acetate for emergency contraception. However, during the assessment of the variation the CHMP considered that number of exposed pregnancies was still very limited. The MAH has therefore provided additional data that are discussed in section 2.5 (third criterion) of this report.

2.5. Assessment of non-prescription status

2.5.1. Background information as provided by the MAH

EC must be used as soon as possible after unprotected intercourse to maximize the likelihood of preventing ovulation and thereby preventing an unwanted pregnancy.

A decade of experience with levonorgestrel EC has shown that pharmacy access enables women to quickly use EC. In 2005, the council of Europe included levonorgestrel 1.5 mg in the list of medicinal products exempt from prescription.

It has also been demonstrated that women can appropriately use EC without medical supervision.

Clinical and biological evidence demonstrates that ulipristal acetate 30 mg is more effective than levonorgestrel, especially when taken within the first 24 hours after intercourse, at the time when the vast majority of women ask for EC. The adverse event profiles of ulipristal acetate and levonorgestrel are comparable, and no safety signal has been detected during clinical development or marketing of ulipristal acetate. The MAH therefore argued that ulipristal acetate 30 mg should therefore be equally accessible without prescription. As long as ulipristal acetate 30 mg is subject to medical prescription, women cannot optimally benefit from its advantages versus levonorgestrel, because the vast majority of women go directly to the pharmacy when they need EC. Most pharmacists do not refer women to a physician for ulipristal acetate because this would delay the use of EC.

Therefore, the MAH is of the opinion that it is in both individual women's and public health interest that women requesting EC after unprotected intercourse can be promptly offered ulipristal acetate 30 mg to get the best chance of preventing an unwanted pregnancy; only pharmacy access will ensure that every woman can access it as early as possible after unprotected intercourse.

2.5.2. Additional benefit for ellaOne in a non-prescription setting

The MAH has utilised a semi-quantitative methodology for evaluating the benefit-risk balance of ellaOne in an OTC setting. This overview has been taken into account in the assessment of the switch in prescription status, but is considered supportive evidence and was not discussed in detail.

This methodology, which is first presented by Brass et al in 2011, is evaluating the benefit of the product from a public health point of view rather than an individual level. Factors such as “number of unintended pregnancies,” “its public health consequences,” and “cost to health systems” are the criteria for effectiveness. The risk, however, naturally involves the individuals rather than the system, taking into account factors such as “use in pregnancy” and “overdose.”
In general, this methodology provides a good insight to the benefit-risk balance of the product in an OTC setting. The MAH concluded that in this analysis potential benefits of ellaOne switch to non-prescription outweigh the risks.

2.5.3. Legal status – Analysis of ellaOne with respect to the four criteria of the European Commission Guideline

The MAH requested the supply of ellaOne to be classified as “not subject to medical prescription” meaning that the criteria of Article 71 of Directive 2001/83/EC, as amended, do not longer apply to ellaOne for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure. For the assessment of this request, the criteria as laid down in the European Commission Guideline on changing the classification for the supply of a medicinal product for human use (European Commission, 2006 revision) apply.

First criterion: Direct or indirect danger, even when used correctly, if utilised without medical supervision

The following data have been provided by the MAH:

(1.1) the absence of direct danger and the acceptable safety profile of ellaOne

EllaOne is taken as a single dose immediate-release tablet that is absorbed within one hour and fully eliminated within one week of dosing. Any drug-related side effects would be expected to occur rapidly and resolve quickly after intake, as has indeed been observed in clinical trials.

Toxicity profile

The toxicity of ulipristal acetate has been thoroughly investigated in a complete preclinical package. Ulipristal acetate is a selective progesterone receptor modulator acting on the progesterone receptor, with limited cross-reactivity on other steroid receptors including glucocorticoid receptors.
Ulipristal acetate is not genotoxic. It displays a low general toxicity with toxicological profile resulting from its pharmacological activity. It is not teratogenic.

Clinical safety profile

The clinical safety profile of ulipristal acetate has been thoroughly investigated during clinical trials conducted to support the registration of ellaOne 30 mg tablet for EC (single administration) in a representative population of the EC users and to support the registration of Esmya 5 mg tablets for the treatment of symptoms of uterine fibroids (daily administration during 3 months, company Gedeon Richter). Available clinical evidence also includes post-marketing experience data collected since ellaOne launch (estimation of 3 million exposed).

This safety profile is also to be assessed in the context of the use of this medication. As per its indication, ellaOne is a single use medication. Despite the occurrence of very frequent episodes of unprotected intercourse and despite the transition of EC to non-prescription ten years ago, EC remains infrequently used by women. A number of studies in women presenting for abortion with an unwanted pregnancy have shown that only 3% of women in Sweden, 5% in Spain, 9% in France and 12% in the UK had used EC to try to prevent this unwanted pregnancy with EC (Moreau 2005, Glasier 2006, ACAI 2010). Among the general population, use is considerably less: for instance, 7% of young women aged 16-19 and less than 1% of all other age groups in the UK (Lader 2009). As a consequence, for a single individual, the life-time exposure to this medication is likely to be low.

Even though ellaOne is used as a single administration of 30 mg ulipristal acetate for EC, it is useful to cite supportive data from studies of chronic use at 5 or 10 mg per day for several months, which have not identified any safety signal.

In conclusion, the sizeable available data on ulipristal acetate collected in a variety of regions and ethnic groups representative of Western populations shows that no safety signal has been identified. This has been confirmed over the last 6 PSURs. EllaOne has a safety profile comparable to levonorgestrel, the most widely accessible and most frequently used EC product in Europe.

(1.2) the absence of indirect danger if ellaOne were used without medical supervision, and the importance of timely use in order not to jeopardize treatment success

EllaOne is a single intake treatment and is not a symptomatic treatment that might as a consequence mask or hide an underlying condition requiring medical attention.

It has been demonstrated that women who ovulate shortly after unprotected intercourse stand the highest chance of becoming pregnant; therefore EC needs to be accessible for prompt intake to optimize the chances of stopping ovulation before it happens. If EC is not used in time, there is greater risk to jeopardize the success of the treatment and data from numerous trials have shown that when women do not need to see a doctor to get a prescription (Raymond 2006, Ekstrand 2008, Black 2008, Rubin 2011), they use it sooner after intercourse.
Experience with the non-prescription use of levonorgestrel EC provides reassuring evidence that pharmacy access has not created any particular indirect danger. Particularly, studies that have examined the use of EC when provided directly at the pharmacy or given in advance of need, have shown that, compared to prescription provision, direct access:

- does not increase sexual risk taking behaviour in adolescents (Ekstrand 2008, Harper 2008, Raine 2012);
- does not lead to increased frequency of unprotected intercourse (Marston 2005, Moreau 2006);
- does not lead to decreased use of effective methods of contraception (Marston 2005, Raine 2005, Ziebland 2005, Moreau 2006, Ekstrand 2008, Moreau 2008) and women's EC experience is actually described as a motivating factor leading to more consistent use of regular contraception (Gainer 2003);
- does not lead to increased rates of sexually transmitted infections (Raymond 2006, Raine 2005).

(1.3) the ability of targeted users to correctly diagnose the indication for use (unprotected intercourse)

EC is indicated for use after unprotected sex or contraceptive failure (e.g. a condom accident or missed pill) in order to prevent unintended pregnancy. Only the woman herself can conclude that she is at risk of unintended pregnancy, and a health professional can only become aware if the woman signals that such is the case.

(1.4) risk and consequences of incorrect use

The conditions of potential incorrect use of ellaOne correspond to very rare situations in the target population and the danger to health if the product is incorrectly used is small. The likelihood and clinical consequence of possible incorrect use of the drug (either because the user has a condition listed under precautions or warnings or uses it outside the indicated timeframe, or because the user has concomitantly been treated with an interacting drug) has been reviewed by the MAH.
The MAH has reviewed the likelihood and clinical consequence of usage of interacting drugs, and proposed risk mitigation strategy for:
- Use as regular contraception
- Use more than 5 days after unprotected sexual intercourse
- Intake during pregnancy
- Breastfeeding in the week following ellaOne intake
- Use in women with severe asthma treated with oral glucocorticoid
- Use in women with severe hepatic impairment
- Concomitant intake of levonorgestrel EC for same UPI
- Concomitant intake of regular hormonal contraception
- Use with CYP3A4 inducers

The proposal from the MAH was to strengthen the information provided in the SmPC and Package Leaflet.

(1.5) the adequacy of the proposed patient information to provide guidance on appropriate use of ellaOne in a non-prescription setting

The MAH has revised the different sections of the Product Information to a non-prescription setting in order to provide necessary guidance to women, while minimizing risk and maximizing benefit.

The MAH states that availability of ellaOne as a non-prescription product, when combined with greater information provided to women, would serve to increase awareness and utilization of all EC options. Pharmacist education would also be an important objective as pharmacists would become the primary point of contact for women seeking the product.

The Applicant proposes a revised product information for ellaOne adapted to the non-prescription setting.

Discussion by the CHMP about first criteria

Article 71 of Directive 2001/83/EC and Guideline on changing the classification for the supply of a medicinal product foresee that medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision.

The CHMP has considered the safety profile of ellaOne in order to ensure that it is not likely to present a danger, either directly or indirectly, even when used correctly, if utilised without medical supervision.

With regards to the absence of direct danger, the CHMP agreed with the fact that the safety of ellaOne has thoroughly been investigated in the studies at time of the initial marketing authorisation. These data are now extended by a study on repeated administration (HRA2914-554; every 5 days and every 7 days) and a study in adolescents (HRA2914-515). The data of these studies confirm the positive benefit/risk ratio of ellaOne.

Article 71 of Directive 2001/83/EC and the Guideline on changing the classification for the supply of a medicinal product also mention that the safety of a medicinal product subject to a switch to a non-prescription status has to be relative to that of the alternative treatment. The safety profile of ellaOne is comparable with levonorgestrel.

Based on this safety profile, the CHMP considered that ellaOne is not likely to present a direct danger even when used correctly, if utilised without medical supervision.

With regards to the absence of indirect danger, the CHMP agreed that EllaOne is a single intake treatment and is not a symptomatic treatment that might as a consequence mask or hide an underlying condition requiring medical attention. Moreover, the importance of a timely use in order not to jeopardise the treatment success, the CHMP agreed with the MAH that ellaOne could benefit from a non-prescription status, as the accessibility to ellaOne will be easier with such a change in status. This is important as after unprotected intercourse women should take EC as soon as possible. The advantage of ellaOne compared to levonorgestrel is that ellaOne can be taken up to 120 hours after unprotected intercourse in contrast to levonorgestrel 1.5 mg, which is registered for up to 72 hours after unprotected intercourse. Moreover, a meta-analysis (HRA2914-541) on the results of the HRA2914-507 and HRA2914-513 studies show a lower pregnancy rate after ellaOne intake compared to levonorgestrel in the time window 0-72 hours.

Article 71 of Directive 2001/83/EC and the Guideline also foresee that the condition should be correctly self-assessed by the patient. EC is indicated for use after unprotected sex or contraceptive failure (e.g. a condom accident or missed pill) in order to prevent unintended pregnancy and therefore the CHMP agrees that the woman can correctly self-assessed that she is at risk of unintended pregnancy.

The CHMP considered that the risk and consequences of incorrect use are indeed small as assessed by the MAH and can be effectively addressed by strengthening the information presented in the Package leaflet and SmPC.

As to the patient information, the written information (package leaflet and label) has been updated and the CHMP considered that the changes were adequate to contribute effectively to safe and effective use of the medicine. The information on the correct use of the medicine is explained in the proposed Package Leaflet. In order to ensure that this information on how to use the medicine appropriately is clear enough for the patients, a readability testing has been performed among representatives of the target population. The criterion of Readability guideline has been met, i.e. a satisfactory test outcome was achieved as the information requested within the package leaflet could be found by 90% of test participants, of whom 90% could show that they understand it. The study questions achieved 17/20 correct answers or more, which show that the criteria has been met.

The need for additional risk minimisation measures (educational material for pharmacists and patients) was discussed between the MAH and the CHMP. The Product Information has been updated adequately to reflect information and guidance relevant to a switch to a non-prescription status and ensure the safe and effective use of the medicine in that setting. Therefore the CHMP considered this update as sufficient to minimise the risks and that no additional risk minimisation measures was needed.

Conclusion by the CHMP about first criteria

In view of the above discussion, the CHMP considered that Criterion 1 of the Article 71 of Directive 2001/83/EC and European Commission Guideline “Medicinal products shall be subject to medical

prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision" does not apply.

Second criterion: Known incorrect use

The MAH presented the following data supporting the fact that this criterion does not apply:

(2.1) potential incorrect use is unlikely and manageable by the proposed risk mitigation strategy

The conditions of potential incorrect use of ellaOne correspond to very rare situations in the target population and the danger to health if the product is incorrectly used is small. The likelihood and clinical consequence of possible incorrect use of the drug (either because the user has a condition listed under precautions or warnings or uses it outside the indicated timeframe, or because the user has concomitantly been treated with an interacting drug) has been reviewed by the MAH and risk mitigation strategy to minimize the risks were proposed. Moreover, experience with levonorgestrel EC has shown that the product can clearly be used easily, safely and correctly and has not led to any safety concerns. The instructions for use of ellaOne are very similar to those of levonorgestrel.

The MAH has also undertook a survey in 5 European countries (France, Spain and UK where women in vast majority seek EC directly in pharmacy; Germany and Italy where they need a prescription to obtain EC) to describe the current user patterns of EC (BVA Healthcare 2012 (HRA2914-557)). More than 10 thousand women were recruited as a representative sample of the reproductive age female population in each country. Median age of EC users was 26 to 29 years, showing that the EC user population does not only include very young women. The majority of women had no children (50-70%), 35-45% had 1 or 2 children except in France where they were only 24%. Women who had used EC in the past year had in majority finished secondary school and had some university level education, only 1-12% had not finished secondary school. In all countries, more than 80% of women took EC in the first 24 hours following unprotected intercourse. Nine to 12% waited until the second day. Approximately 2% took EC after 72 hours of unprotected intercourse, indicating that spontaneously women tend not to wait after unprotected intercourse to seek EC.

In a Request for Supplementary Information (RSI), the CHMP raised a concern that ulipristal acetate could be used off-label as it may be perceived as a possible abortifacient on the basis of its pharmacodynamic properties. The MAH provided the following data in answer to the RSI.

1 Clinical and post-marketing experience demonstrate that UPA is neither perceived nor utilized as an abortifacient; there have been no reports of attempts to use it with such intent. Indeed, selective progesterone receptor modulators are used in a variety of reproductive health indications and are not necessarily perceived as drugs for medication abortion

1.1 UPA is neither perceived nor utilized as an abortifacient

A concern that ellaOne might be perceived as a possible abortifacient by physicians, and therefore potentially be used as such, was raised during the initial procedure for marketing authorisation. Subsequent 'real world' evidence is reassuring. This concern has not come true in reality. Today, after four years on the market, ellaOne is neither perceived as an abortifacient nor prescribed with such intent.

Healthcare professionals prescribe ellaOne in line with the license. In addition to the results already reported for Portugal, France, UK, Germany, Poland and Sweden (HRA2914-552 and HRA2914-544), new data from Poland and Sweden (HRA2914-544a) on the off-label prescription of ellaOne showed:

- Of 75 prescribers interviewed in both countries, 20% recalled having prescribed ellaOne more than 5 days after unprotected intercourse (UPI). The main reason given for off-label prescription was uncertainty over the time since UPI.
- 2.7% prescribed more than one dose of ellaOne at once, because of risk of vomiting.

When healthcare professionals were asked (HRA2914-544a) for the reasons of off-label prescription, they unanimously responded that they had never prescribed ellaOne with the intent of terminating an existing pregnancy.

The study demonstrates that off-label prescription of ellaOne for abortion does not happen in the real world, dispelling the concern that existed prior to the approval of the original Marketing Authorisation.

1.2 Selective progesterone receptor modulators are used in a variety of reproductive health indications and are not necessarily perceived as drugs for medication abortion

UPA belongs to the family of Selective Progesterone Receptor Modulators (SPRM). The structure of SPRMs is believed to generate a specific conformation of the progesterone receptor resulting in a broad spectrum of mixed agonist/antagonist activity (Madauss *et al* 2007, Chabbert-Buffet *et al* 2012).

As such, UPA shares characteristics with other compounds including onapristone, asoprisnil, telapristone and mifepristone.
Despite a historical delay in the development of SPRMs, due to a negative image of mifepristone related to abortion (Chabbert-Buffet *et al* 2008), these compounds have more recently been investigated, or are marketed, for diverse clinical indications. They are particularly associated with gynaecological disorders and contraception. For example, UPA is also marketed for treatment of uterine fibroids, and other SPRMs have been investigated for myoma-related excess bleeding and pelvic pain. (Chabbert-Buffet *et al* 2012, Pintiaux *et al* 2009)

The only compound that has been proven to induce pregnancy loss in a clinical setting is mifepristone (RU486) in combination with a prostaglandin agonist and is approved and marketed for the medical termination of pregnancy in 19 EU countries. The licensed dosage and mode of administration of mifepristone for the termination of pregnancy up to 49 days of amenorrhea is 600 mg orally (followed 36 to 48 hours later, by the administration of a prostaglandin analogue misoprostol 400 µg orally, or gemeprost 1 mg per vaginam) or up to 63 days of amenorrhea in association with gemeprost 1 mg per vaginam. Alternatively, single oral dose of 200 mg mifepristone may be used in association with gemeprost 1 mg per vaginam.

"Mifepristone is the only SPRM used for pregnancy termination because of its unique ability to terminate pregnancy in women. Other SPRMs have not been studied for this indication." (Bouchard *et al* 2011). Since its discovery in 1980 and for the subsequent 15 to 20 years, agonistic effects of mifepristone have not been taken into account and the product has been described and perceived by the vast majority of healthcare professionals as a pure progesterone antagonist. It is only in the late 1990s that molecules with various mixed agonist/antagonist ratios have been recognized, leading thereby to the denomination of SPRMs. Mifepristone was subsequently added to this class of products (Elger *et al* 2000). Nevertheless, for the few SPRM specialists, mifepristone agonist properties are recognized as marginal, with mifepristone acting as a progesterone antagonist in most circumstances (Spitz *et al* 2000). Therefore, mifepristone is still perceived by most healthcare professionals as an antiprogesterone and the denomination SPRM is essentially used for molecules developed more recently (e.g. UPA, asoprisnil).

In conclusion, an abortifacient image is not the hallmark of all SPRMs. It is specifically and strongly associated with mifepristone. (Bouchard *et al* 2011, Chabbert-Buffet N *et al* 2012).

2 No abortifacient effects have been reported at any dose or with any duration of therapy in the clinical setting. Therefore, only animal data can be used to inform the question of abortifacient potency. When extrapolated to the clinical setting, available animal data concur that abortifacient effects could only ensue with exceedingly high doses.

UPA has never been investigated for clinical abortion nor have there been any reports of abortifacient effects in women at any dose or with any duration of therapy. Whether and at what dose UPA might induce pregnancy loss in women is unknown. Therefore, only animal data can be used to inform the question of abortifacient potency.
Two animal studies (HRA2914-407 and HRA2914-409) in the nonclinical data package are of particular relevance to estimate the potency of UPA to induce pregnancy loss in humans. Both studies evaluated fetal loss and used mifepristone used as an active control arm. In order to allow extrapolation from animal to human, doses were normalised relative to the body surface area of animals as recommended in the FDA guidance: "Estimating the Maximum Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers". For information, the dose of UPA in ellaOne (30 mg) corresponds to 18 mg/m² and the minimum approved dose of mifepristone for medical termination of pregnancy (200 mg) corresponds to 125 mg/m² [calculated for a woman weighing 60 kg, according to the FDA guidance].

In the first study (HRA2914-409) in primates (Macaca fascicularis), the agents were administered orally to groups of 5 pregnant animals at two doses (0.5 and 5 mg/kg/day) for 4 days. Dosing took place in the early days of gestation, within the two weeks following embryonic implantation, from gestation days (GD) 23 to GD 26. The results from this study are summarised in Table 16 with the calculations done to allow comparison between monkey and human.

Table 16: Effects in early gestation in monkeys (study HRA2914-409)

Admin.	Gestation day dosing	Dose		# animal aborted / # animal treated	
		Daily dose (mg/kg/day)	Cumulative dose (mg/m²)	Mifepristone	UPA
Oral; 4 days	GD23 to GD26	0.5	24	**2/5 (40%)**	0/5 (0%)
		5	240	4/5 (80%)	**2/5 (40%)**

(a) **Minimal effective dose (MED) in bold**
(b) Since dosing was repeated for four consecutive days, and considering the relative long half-life of UPA and mifepristone (several hours), cumulative doses are shown in the table

In the other study (HRA2914-407), guinea pigs were dosed with different doses of the agents (3, 10 and 30 mg/animal/day) for two consecutive days in the last third of the gestation period (GD43 to GD44). The results from this study are summarized in Table 17 and the same calculations done to allow comparison between guinea pig and human.

Table 17: Effects in late gestation in guinea pigs (study HRA2914-407)

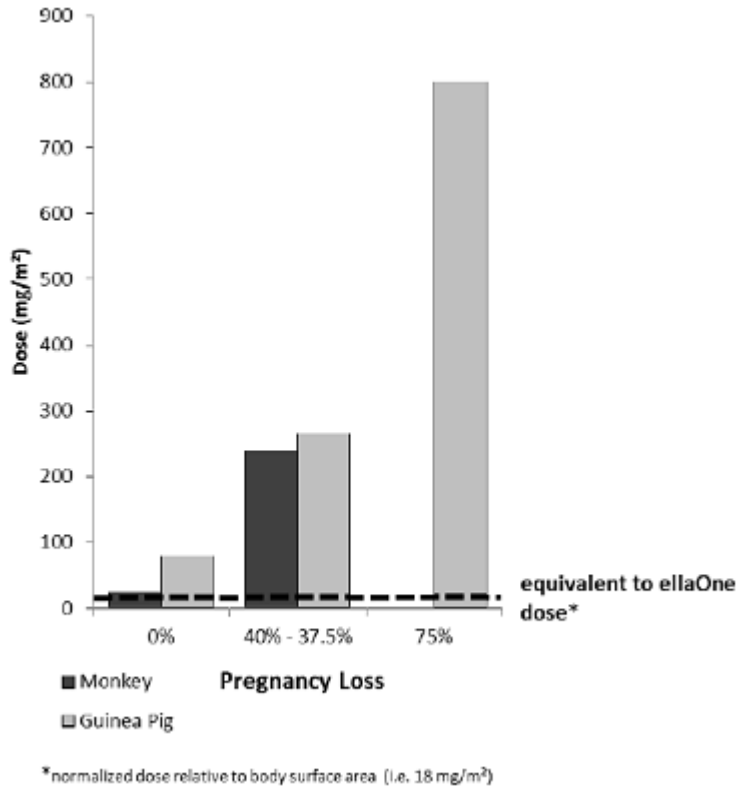
Admin.	Gestation day dosing	Dose		# animal aborted / # animal treated	
		Daily dose (mg/kg/day)	Cumulative dose (mg/m²)	Mifepristone	UPA
SC; 2 days	GD43 – GD44	5	80	**3/8 (37.5%)**	0/8 (0%)
		17	264	4/8 (50%)	**3/8 (37.5%)**
		50	800	6/8 (75%)	6/8 (75%)

(a) **Minimal effective dose (MED) in bold**
(b) Since dosing was repeated for two consecutive days, and considering the relative long half-life of UPA and mifepristone (several hours), cumulative doses are shown in the table

Although the doses investigated in these studies remain limited, the data are consistent across the studies, similar between the two animal species considered and the gestational age.

When relative potency data are extrapolated to determine a possible clinical dose, with all caveats regarding animal-to-clinical dose extrapolation, the results may suggest that the dose needed to induce a pregnancy loss in some women would be at least 13 times the 30 mg dose. In this extrapolation, it has not been taken into account that in women mifepristone always needs to be taken in combination with a prostaglandin to be effective.

Figure 3: Cumulative doses of UPA in relation to foetal loss in two animal species



For medical termination of pregnancy, the minimum dose of mifepristone approved is 200 mg. No clinical comparison of the relative potency of UPA and mifepristone is available in any indication. In the above-mentioned animal studies of foetal loss, UPA was three times less potent than mifepristone in guinea pigs (late gestation exposure) and ten times less potent in monkeys (early gestation exposure).

Table 18: Comparison of UPA and mifepristone effects in early and late gestation in monkeys and guinea pigs (studies HRA2914-409 and HRA 2914-407)

Species	Administration	Gestation stage	Abortifacient relative potency (MED UPA/MED Mife)
Monkey	Oral; 4 days	Early	10
Guinea pig	SC; 2 days	Late	3.3

Abortifacient Relative Potency: the highest the ratio, the lowest the potency of UPA

Whether, and at what dose, UPA might induce pregnancy loss in women is unknown. Extrapolation from both data sets concurs that exceedingly high doses of UPA would be required before any such effects would ensue.

3 It is unlikely that attempts to misuse ellaOne with abortifacient intent would be frequent or widespread if the product were available on a non-prescription basis

3.1 The vast majority of women in the EU have legal access to abortion

Abortions are performed in all regions of the world, regardless of the status of abortion laws. Unintended pregnancies occur in all societies, and if regulated abortion services are not readily available, distressed women may resort to unsafe abortions (Sedgh G *et al* 2012). Across nearly all the European Union, the incidence of unsafe abortion is negligible (WHO 2008).

In most European Union member states elective abortion is legal (Gissler *et al* 2012). However, in Malta and Andorra, abortion is illegal on any grounds. In Poland, abortion is legal only to save the life of a woman. In Ireland, the abortion laws have recently been changed to provide for a woman's right to an abortion if her life is at risk.

Therefore the overall population of women susceptible to resorting to illegal abortion in the EU is very limited.

3.2 Where legal access to abortion services is not available, women travel to countries where legal services are available to them

Many women in the countries with severe restrictions access regulated services by travelling abroad to countries where elective abortion is legal. (Johnston *et al* 2012). Statistics reported by the UK NHS show that in 2008, 4,600 women providing Irish addresses had an abortion in the UK. This figure probably underestimates the true incidence, as not all women resident in the Republic of Ireland provided their Irish address for reasons of confidentiality (Koffeman *et al* 2010). An increasing number of women also travel to other EU countries such as the Netherlands (Koffeman *et al* 2010).

3.3 Illegal abortions, whilst rare in the EU, are to a large extent carried out under medical supervision, and ellaOne is not perceived or used as a pharmaceutical for inducing illegal abortion by healthcare professionals

The remaining, very few women, who are unable to obtain access legal abortion services are at risk of resorting to illegal abortion.

A thorough review of the literature on abortion in the four European countries, where this procedure is essentially illegal found reports describing situations of illegal abortion in Poland. No such reports were identified for Malta or Andorra, and as described above, in the case of Ireland multiple sources refer to women travelling to the UK or continental Europe to seek abortion services. Reports from Poland describe women obtaining healthcare professional-delivered abortion through an 'abortion underground'. In total, an estimated 150,000 abortions are performed by healthcare professionals per year and, while illegal, are not unsafe (Chelstowska *et al* 2011).

As described in point 1.1 above, ellaOne is prescribed normally for emergency contraception. It is neither perceived nor used by healthcare professionals as a pharmaceutical for inducing illegal abortion (HRA2914-544a).

3.4 Even for the minority of women in the EU who do not have access to abortion services delivered by healthcare professionals under medical supervision, ellaOne is an unrealistic option

Women who do not have access to abortion services but want to terminate their pregnancy by themselves find information about their options on the internet (Zamberlin *et al* 2012). Extensive information is readily accessible online about how to perform medication abortion with mifepristone and misoprostol. Although these medicinal products are not readily available in pharmacies, they can be obtained on the Internet.

In contrast, no abortifacient effects have been reported at any dose of UPA or with any duration of therapy in the clinical setting. If women search for methods of abortion they will not be led to any specific information about ellaOne in this regard. In the absence of any clinical data to guide the regimen to be used, a woman could take any number of tablets. The risks of such misuse are deemed low by the MAH.

Discussion by the CHMP about second criteria

The risk on off-label use should be considered when the product will be available without a prescription. It is important that the product will be used according to the indication, i.e. within 120 hours after unprotected intercourse.

Therefore during the evaluation process of the ellaOne registration dossier the MAH was requested to study any potential off-label use of ellaOne, in particular during pregnancy possibly as an abortifacient. No clinical studies have been performed with ulipristal acetate as an abortifacient, and it is therefore also unknown whether it is possible to use it for abortion. As to the extrapolations from animal data performed by the MAH to inform the question of abortifacient potency, it was not clear to the CHMP on what basis the dose of 13 times 30 mg was calculated. Overall, the dose intervals and group sizes were too limited to base such calculations on, but the main conclusion that can be drawn is that based on extrapolations from these non-clinical data, ulipristal acetate is far less potent compared to mifepristone. Therefore, the dose of ulipristal acetate needed for abortion (if at all possible) would be expected to be higher than for mifepristone (200 mg), and therefore the dose would be much higher than the ellaOne dose of 30 mg. In these extrapolations, it has also not been taken into account that in women mifepristone always needs to be taken in combination with a prostaglandin to be effective.

In addition, the MAH performed a qualitative survey (interviews with 90 HCPs), a quantitative survey (questionnaires with 315 HCPs) and evaluation of patient cases (1233 patient cases were reviewed; 5 most recent patient cases of each 315 HCPs). Results from the 315 surveyed HCPs showed that not all HCPs did know the difference between abortion and emergency contraception. Due to inconsistencies between the results, the MAH was asked to repeat the study on any potential off-label use of ellaOne in Poland and Sweden utilizing a new sample of HCPs, and discuss the results. The results of this study did not indicate that the level of ellaOne off-label prescription is higher in Poland or Sweden compared with the other EU countries studies previously. There was no indication that ellaOne is used as an abortifacient, however use outside the time window of the indication (> 5 days after UPI) does occur, although the exact period was not studied.

According to the CHMP, the survey HRA2914-557 shows that more than 80% of the women take EC within the first 24 hours after unprotected intercourse. This is in line with the recommendation in the SmPCs of both ECs, since the best efficacy is obtained when EC is taken as soon as possible after unprotected intercourse.

Conclusion by the CHMP about second criteria

Article 71 of Directive 2001/83/EC and Criterion 2 of the European Commission Guideline foresee that "Medicinal products shall be subject to medical prescription when they are frequently and to a very

wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health".

In considering whether this criterion applies, the known incorrect use of the medicinal product should be addressed. Therefore the CHMP has considered the potential off-label use of ellaOne, in particular during pregnancy possibly as an abortifacient. Based on the data provided by the MAH, the CHMP did not foresee ellaOne as being frequently and to a very wide extent used incorrectly as an abortifacient in a non-prescription setting and as a result did not consider that the change of classification of ellaOne from prescription to non-prescription status is likely to present a direct or indirect danger to human health.

The following arguments are in support:

- UPA is neither perceived nor utilized as an abortifacient.
  The MAH have performed a prescription study (HRA2914-544 and HRA2914-554a) with healthcare professionals indicating that they had never prescribed ellaOne with the intent of terminating an existing pregnancy; this is reassuring. Further, it is agreed with the MAH that selective progesterone receptor modulators (SPRM) are used in a variety of reproductive health indications and are not necessarily perceived as drugs for inducing abortion. As such, ulipristal acetate - in a dose of 5 mg daily (Esmya) - is approved for uterine fibroids. Moreover, the only SPRM that is marketed and perceived, as an abortifacient for terminating pregnancy is mifepristone in 19 EU countries.

- Only animal data can be used to inform the question of abortifacient potency. Based on extrapolations from these non-clinical data it can be concluded that ulipristal acetate is far less potent compared to mifepristone. Therefore, the dose of ulipristal acetate needed for abortion (if at all possible) would be expected to be higher than for mifepristone (200 mg), and therefore the dose would be much higher than the ellaOne dose of 30 mg. In these extrapolations, it has also not been taken into account that in women mifepristone for medical abortion always needs to be taken in combination with a prostaglandin analogue to be effective.

- Abortion is legal in most EU countries.

Based on these information, the CHMP considered that it is unlikely that attempts to misuse ellaOne with abortifacient intent would be frequent or widespread if the product were available on a non-prescription basis and that criteria 2 did not apply to ellaOne.

Third criterion: Activity or side-effects which require further investigation

According to Article 71 of Directive 2001/83/EC and the Guideline on changing the classification for the supply of a medicinal product, medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side-effects of which require further investigation.
The MAH presented the following data supporting the fact that this criterion does not apply:

(3.1) The pharmacological activity and side effects of ellaOne have been thoroughly characterized, and no significant safety findings have been identified. More than 4,600 Western women have participated in clinical studies. The design of the phase III studies was aimed to assess as many categories of women as possible (e.g. contrary to standard practice to evaluate the efficacy of contraceptives, there was no upper limit for body weight or BMI).
Knowing that ellaOne is a single dose treatment that is rapidly absorbed and eliminated (circulating levels reduced by more than 90% after 7 days), it is reasonable to consider that

drug related side effects should occur rapidly after intake. Therefore, the probability of having reported most of the related side effects that may have occurred during development is high. Overall the activity and side effects of ellaOne have been well described. The most frequently side effects were headache, nausea and abdominal pain. Side effects were mild to moderate and resolved spontaneously. No relevant safety findings have been observed from the whole development. There is no safety signal outstanding that warrants specific further investigation.

(3.2) Post-marketing studies have brought additional evidence to further substantiate the characterization of ellaOne. The repeated use study (HRA2914-554) and the observational study in adolescents (HRA2914-515) provide important new data in view of the reclassification of ellaOne to confirm that the benefit / risk ratio of ellaOne is positive in the target population of EC users. Additional data in adolescents is of particular importance for this reclassification application since EC is of particular importance in this population particularly vulnerable in case of unintended pregnancy.

(3.3) All data generated during development and collected since launch have consistently confirmed the positive benefit/risk ratio.

The MAH proposed to remove the contraindication in pregnancy based on the following grounds:

EllaOne is intended to prevent pregnancy and is clearly not intended for use during pregnancy. Regardless of the EC method, intake during pregnancy is extremely rare in clinical studies as well as in post-marketing experience. In the Phase III clinical program, 0.4% of all subjects were excluded as screen failure because of positive urinary pregnancy test and 0.1% took EC and were subsequently found to have been pregnant when the drug was administered.

According to the MAH, a sizeable pregnancy database is now available which allows omitting the pregnancy contraindication in the ellaOne PI.

Preclinical data substantiate the information collected in humans: there was no relevant risk identified from non-clinical studies. During embryofoetal development, two studies were conducted in rats and rabbits with repeated daily administration for the whole duration of organ formation and development. There was no indication of any teratogenic effect. In addition, no adverse effects on pup development were observed following repeated administration of ulipristal acetate in rats and monkeys during gestation.

Following the decision tree proposed in the Guideline on “Risk assessment of medicinal products on human reproduction and lactation: from data to labelling” (EMEA/CHMP/203927/2005), the pregnancy contraindication is not applicable. Nevertheless, as pregnancy is a specific area of interest for all medications used for fertility regulation, the MAH monitors carefully cases of pregnancy and will pursue its special efforts to collect additional information on this topic: a series of additional actions have recently been agreed with the CHMP to strengthen the collection of pregnancy cases after ellaOne, including the introduction of electronic applications to facilitate case reporting and the possibility for women to report a pregnancy directly.

Two major objections were raised by the CHMP during the assessment phase requesting more information on potential embryofoetal toxicity from the MAH before reclassification could be considered.

The first major objection was the following:
“There is a concern on the effects of ulipristal in case pregnancy exists, at the time when ulipristal is administered. Pregnancy data after exposure to ellaOne are limited and make the change of legal status premature at this stage. More data from the pregnancy registry (MEA 006) need to be obtained first before switching. Thus, criterion 3 of Article 71 of Directive 2001/83/EC and the European

Commission Guideline on changing the classification for the supply of a medicinal product for human use applies. The MAH is asked to comment."

The second major objection was the following:
Further information on potential embryofoetal toxicity is required before the change in classification to non-prescription' can be considered. The following should be taken into account:

- The number of exposed pregnancy outcomes currently available is considered insufficient evidence of an absence of adverse effects in the foetus after exposure to ulipristal during pregnancy.
- Widening access to the non-prescription setting might increase the potential for late usage and enhance the possibility that a woman is already pregnant when exposed to ulipristal.

The MAH should provide sufficient reassurance on lack of negative effects to the foetus after uterine exposure to ulipristal (including teratogenicity) based on non-clinical and clinical data available. Within this context it should be discussed further whether or not pregnancy should be considered as a contraindication.

In their response to the above major objections, the MAH provided the following data:

1 Non-clinical data on the embryo, foetus and offspring after exposure to ulipristal acetate during gestation show that it is not teratogenic

1.1 Ulipristal acetate teratogenicity potential was rigorously investigated in validated animal models before authorisation as a prescription medicine

Animal models have been validated for use to assess the safety and efficacy of steroid hormone contraceptives including UPA. UPA shows high affinity for progesterone receptors from both human and animal species and was reported to efficiently prevent ovulation after a single oral dose in rats and mice, analogously to humans.
The structure, function and expression of progesterone receptors are remarkably well-conserved across species and the preeminent role of progesterone in female reproductive activities has been recognised in rodents and humans. However, subtle variations in the response to progesterone may be observed due to physiological specificity and sensitivity of each species. Regarding maintenance of pregnancy, the rat model is extremely sensitive to small changes in progesterone levels during a critical window of a few days early in gestation, around implantation (Morishige 1973, Arkaravichien 1990). In light of such high sensitivity, Maier and Herman (2001) concluded that data obtained in rodents should be translated to human pregnancy only with caution because any issues seen in rats may be *less likely* in humans.
For obvious ethical reasons the effects of drugs on embryos can be experimentally assessed only in animals. In this regard, the potential effects of UPA on the foetus have been thoroughly investigated in several studies included in the Reproductive and Developmental Toxicity programme submitted in the MA application. These studies focused not only on embryofoetal development, but also on possible effects on pups from dams which were dosed either during the early days of pregnancy or throughout the whole period of organogenesis.
The studies described here comply with current ICH guidelines in terms of animal species investigated, duration of exposure and number of animals investigated in each study, and the results reflect the most rigorous scientific methodology available for the assessment of any teratogenic effects of UPA exposure on pregnancy.
In comparison with the clinical setting, in which the most likely scenario is inadvertent exposure to the pre-conception oocyte or very early embryo, these studies constitute the most stringent assessment of potential toxicity:

- the treatment protocols entail exposure over several days, as opposed to the short-lived single dose administration in the clinical setting

- the windows of exposure studied include both the post-coital timeframe as well as the entire period of organogenesis, which is the period with greatest sensitivity to teratogenic insults and when most gross anatomic malformations can be induced.

Dosing was repeated for 10 to 13 days, i.e. covering approximately half of the total gestation period in rats and rabbits and including the periods of organogenesis, vs. transient exposure in the clinical setting as mentioned above.

1.2 Embryofoetal developmental toxicity studies show that ulipristal acetate is not teratogenic

The design of the studies investigating the effects of UPA on embryofoetal development is briefly summarized in Table 19.

Table 19: Embryofoetal developmental toxicity programme with ulipristal acetate

Study type	Duration of dosing	Dose levels (mg/kg/day)	Number of animals/group	Total number of exposed animals	Study reference
Pilot rat embryofoetal	GD6-GD15	0, 0.1, 0.3, 1.0, 3.0, 10.0	5	25	HRA2924-443
Rat embryofoetal	GD6-GD17	0, 0.1. 0.3, 1.0	25	75	HRA2914-444
Rabbit embryofoetal	GD6-GD18	0, 0.1, 0.3, 1.0	20	60	HRA2914-445

GD: Gestation day

The first study in the rat (HRA2914-443) was designed to provide guidance on the final doses to be investigated in the pivotal study. Animals were treated for ten days. Although pregnancy could not be maintained at the two highest dose levels, macroscopic examination of the 168 live foetuses from dams exposed to lower doses revealed no external malformations.
This observation was confirmed in the pivotal rat study, in which animals were treated for twelve days (HRA2914-444) and foetuses were examined following Caesarean delivery performed on GD20. In total, more than 700 live foetuses from dams exposed to UPA were examined in this study, including 131 from the high dose group, with no abnormal findings. It was concluded that UPA repeatedly administered during the entire period of organogenesis at doses up to 1 mg/kg/day is not teratogenic.
In the pivotal rabbit study, animals were treated for thirteen days (HRA2914-445) and foetuses were examined following Caesarean delivery performed on GD29. A total number of 340 live foetuses with *in utero* exposure to UPA were examined in this study, including 86 from the high dose group. In agreement with the rat studies, no teratogenic effects of UPA were identified.
Extrapolation from animal doses to human may be done as recommended in the FDA guidance: "Estimating the Maximum Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers", by normalising the doses relative to the body surface area of animals. The dose of UPA in ellaOne (30 mg) corresponds to 18 mg/m² [calculated for a woman weighing 60 kg, according to the FDA guidance]. Taking into account the repeated dosing, cumulative doses may be calculated for a best estimate of total exposure. The normalised cumulative doses are presented in Table 20. The same calculation applied to rabbit data would lead to a maximum exposure of 156 mg/m².

Table 20: Summary of cumulative doses in animal studies

Species	Gestation day	Duration of	Max Daily	Cumulative	Comments

	dosing	dosing (days)	Dose*	dose (mg/m²)	
Rat	GD6 to GD15	10	1 mg/kg/d	60	No teratogenic effects
Rat	GD6 to GD17	12	1 mg/kg/d	72	No teratogenic effects
Rabbit	GD6 to GD18	13	1mg/kg/d	156	No teratogenic effects

GD: Gestation day
*Highest dose allowing embryos or pup evaluation

The MAH concluded that these studies demonstrate that no teratogenic signal is observed in animals following exposure to UPA.

1.3 Repeated administration of ulipristal acetate early during gestation is safe and allows pups to develop normally

Three additional studies conducted in the rat and monkey address the question of whether UPA exposure during pregnancy might have an impact on foetal development. They provide data on pups from dams that were exposed to UPA at different stages and with different durations during gestation and up to weaning. The studies are presented in Table 21.

Table 21: Effects ulipristal acetate on pup development following administration to pregnant rats and monkeys

Study type	Duration of dosing	Dose levels (mg/kg/day)	Number of animals/group	Total number of exposed animals	Study reference
Rat	GD0-GD3	0, 2, 4*	10	20	HRA2914-446
Rat	GD6-L20	0, 0.3, 0.1, 0.3	25	75	HRA2914-471
Monkey	GD23-GD26	0, 0.5, 5	5	10	HRA2914-409

GD: Gestation day; L: Lactation day
* Daily dose: 0.5 and 1 mg/animal in females with mean body weight of ~250 g

In the first study (HRA2914-446), pregnant rats were exposed to UPA in the early days of gestation (days 0-3 post coitum) after mating – a situation analogous to the use of UPA as an emergency contraceptive. The number of pregnant animals was reduced at the high-dose level. Administration of UPA in the early days of gestation did not affect the percentage of live pups born, the ability of pups to survive, the number of pup deaths or the gender ratio of pups. The development of more than 150 pups from UPA-exposed dams was followed up to sexual maturity, and including their reproductive capacity. There was no observed effect on pup body weight development or on the sexual development of females as assessed by the onset of vaginal opening and establishment of normal estrous cycles. Furthermore, there was no effect on the fertility of males or females of this F1 generation. This important study shows that an early exposure to elevated doses of UPA has no deleterious effect on the development of pre-embryos, and has no later consequences on the development and the fertility of pups that were exposed *in utero* to UPA.
Applying the same calculation as explained above, exposures to UPA achieved in the high-dose group are 5-fold in excess of those reached in women after a 30 mg dose of UPA, i.e. 18 mg/m² (Table 22).

Table 22: Summary of cumulative doses in rat and monkey studies

Species	Gestation day dosing	Duration of dosing (days)	Max Daily Dose*	Cumulative dose (mg/m²)	Comments
Rat	GD0 to GD3	4	4 mg/kg/d	96	Normal pup development
Rat	GD6 to L20	16**	0.3 mg/kg	29	Normal pup development
Monkey	GD23 to GD26	4	5 mg/kg/d	240	Normal pup development

GD: Gestation day; L: Lactation day

*Highest dose allowing embryos or pup evaluation

** Only dosing during gestation is considered; parturition occurred at GD21 in most of exposed dams

In addition, in a separate study (HRA2914-421), rats received a single oral dose of UPA 5 mg/kg, a dose very close to the high dose investigated in study HRA2914-446 discussed above. Plasma levels of UPA were measured using a similar LC-MS/MS assay to the one developed for human plasma. The maximal plasma concentration and AUC_{0-t} of UPA at 5 mg/kg were 0.681 µg/mL and 3645 ng.h/mL respectively, to be compared to 0.176µg/mL and 548 ng.h/mL in women receiving 30 mg UPA (HRA2914-504). This study provides further reassurance that the doses of UPA investigated in the rat study HRA2914-446, that proved to be non harmful for the development of the pre-embryo, most likely resulted in exposures in large excess of those reached in women after a 30 mg dose.

In the second study (HRA2914-471), female rats were exposed from day 6 of gestation to weaning (day 20 of lactation inclusive). No abnormalities were reported for more than 800 live pups that were observed at birth. The sexual development, mating performance and fertility of pups that had been exposed *in utero* to each of the doses of UPA (75 males and 75 females) was evaluated. There was no evidence of any adverse outcome on the post-weaning development of the offspring and on their fertility.

The third study was conducted in primates (Macaca fascicularis) (HRA2914-409). Dosing took place in the early days of gestation, within the two weeks following embryonic implantation, from GD23 to GD26. In dams in which pregnancy continued and that were allowed to deliver normally (4 and 2 live births from dams dosed with low and high dose, respectively), there was no evidence of any structural or physiological abnormalities in their offspring. Although animal numbers are small, this does provide further reassurance that foetuses exposed to UPA will develop normally. As shown in Table 22, a 13-fold higher exposure (240 mg/m² vs. 18 mg/m²) was achieved in high-dosed monkeys compared to women taking ellaOne for EC.

1.4 Insights from progesterone receptor knock-out mice demonstrate that suppression of progesterone signalling is not associated with an increased risk of teratogenicity

Mouse mutants carrying a null mutation of the PR gene have been used to elucidate the physiological events that are specifically attributable to progesterone *in vivo*. Adult female progesterone receptor knock-out (PRKO) mice display significant defects in reproductive tissues, underlining the importance of progesterone as a pleiotropic coordinator of reproductive events in sexually mature animals. Earlier in life, however, no such defects have been observed – PRKO embryos of both sexes develop normally to adulthood (Lydon 1995). Anatomical examination did not reveal obvious differences in organ morphology between the homozygotes and their wild-type and heterozygote littermates, indicating that the complete suppression of progesterone signalling from the earliest stage of life does not

compromise normal development of adults; this suggests that transient antagonism of the progesterone receptor in utero via maternal exposure to UPA would be unlikely to pose any risk.

The MAH concluded that non-clinical data from administration of UPA throughout gestation in multiple animal models provides comprehensive reassurance that UPA at doses used for EC:
- Does not result in harm to the embryo or foetus
- Does not induce any teratogenic effect
- Does not compromise the development of offspring who were exposed in utero.

2 Non-clinical data provide reassuring evidence that UPA 30 mg is not embryolethal and that such effect could only ensue with exceedingly high doses

The data summarized above clearly demonstrate that UPA does not harm the embryo and the foetus and does not induce any teratogenic effects. It is important to mention here, as previously demonstrated in the Response to the first Request for Supplementary Information (dated 25 April 2013) submitted in September 2013, that no abortifacient effects have been reported at any dose or with any duration of therapy in the clinical setting. Animal data showed that abortifacient effects would only be observed with exceedingly high doses, when extrapolated to the clinical setting. These data were extensively discussed in the above mentioned Response document and are briefly summarized here.

The potency of UPA to induce foetal loss was investigated in primates and guinea pigs (studies HRA2914-409 and HRA2914-407), and mifepristone was used as an active control arm in both studies. The monkey study investigated the effects of UPA when dosed for four consecutive days in the early days of gestations within the two weeks following implantation, whilst effects on late gestation were analysed in the guinea pigs study, with UPA given for two consecutive days. Whereas 30 mg UPA (one tablet of ellaOne) correspond to 18 mg/m² as explained above, the minimal effective doses of UPA inducing foetal loss in some but not all animals, were 240 and 264 mg/m² (expressed as cumulative dose) in monkeys and guinea pigs respectively. The corresponding minimal effective doses of mifepristone were 24 and 80 mg/m².
These studies therefore showed UPA to be consistently less potent than mifepristone. The results also suggest that the starting dose needed to induce a pregnancy loss in some women would be at least 13 (240/18) times the 30 mg dose. This most conservative figure comes from the monkey data.
The MAH concluded that extrapolation from both data sets concur that exceedingly high doses of UPA would be required to induce pregnancy loss in women.

3 Clinical data on pregnancy after use of ulipristal acetate

3.1 Women using ellaOne take it in the cycle of eventual conception

For women using ellaOne for EC, the most common timing of exposure is during the cycle of conception, as most women seek EC following unprotected intercourse (UPI), but before the onset or delay of menses. At this time, diagnosis of an implanting / very early pregnancy is usually impossible. During the first two weeks after conception, and before the expected date of menses, the developing embryo is not susceptible to teratogenesis (FDA 2005). Drug exposures during this time period are not known to cause congenital anomalies in human embryos; although such exposures may interfere with the cleavage of the zygote or implantation of the blastocyst and/or cause early demise and spontaneous abortion of the embryo (FDA 2005).
In humans, the embryo development is most easily disrupted during the period of organogenesis (3 to 8 weeks post-conception) when tissue and organs are forming; indeed the vast majority (90%) of foetal malformations and subsequent miscarriage occur during this time period rather than later in pregnancy (Brent 2007). For affected embryos which are not miscarried, gross malformations are evident during pre-natal care or at birth.

3.2 After 3 million doses of ellaOne used, a total of 568 pregnancies following ulipristal acetate intake have been reported

Post-marketing data through to 31 August 2014 include pregnancies reported following more than 3 million doses of ellaOne used. The total number of pregnancies following UPA intake, reported either during clinical trials or through post-marketing surveillance, is now 568. Database analysis reveals no evidence of adverse effects of ellaOne exposure in terms of rates of miscarriage or in the normal development and growth of the embryo and foetus through the first trimester and to term.

3.3 The risk of miscarriage is not increased after exposure to ulipristal acetate during early pregnancy or during the cycle of conception. Miscarriages occur well after drug intake (mean delay of 36 days) thereby and therefore are unlikely to be precipitated by drug exposure

Among the 349 cases with known outcome reported (excluding ongoing pregnancy cases with no prenatal morphological ultrasound data available), there were 54 cases of miscarriage or early missed abortion (15.5%) (Table 23). This rate is below the rate of miscarriage in the general population (20%) and below the rate observed in very early pregnancies (including in biochemical pregnancies) when women are not aware of being pregnant, which is best described to be 30% (Wilcox 1988).

Table 23: Miscarriage rate after intake of ulipristal acetate during the cycle of conception

Pregnancy outcome	**Total,** n (%)	**Clinical trials,** n (%)	**Post-marketing,** n (%)
Total pregnancy with known outcome	349	83	266
Total spontaneous abortion & missed abortion	54 (15.5%)	19 (23%)	35 (13%)
Spontaneous abortion	*48 (14%)*	*17 (21%)*	*31 (12%)*
Missed abortion identified at time of induced abortion	*6 (2%)*	*2 (2%)*	*4 (2%)*

Miscarriages occur well after drug intake (mean delay of 36 days) and therefore are unlikely to be precipitated by drug exposure (Table 24). For those miscarriages which occurred following intake during a confirmed pre-existing pregnancy, the rate was 10.4% (including one case of missed abortion), with a mean time between intake and outcome of 21 days at a mean GA of 44 days (not shown in Table 24).

Table 24: Miscarriages after intake of ulipristal acetate: time from intake and gestational age at the time of outcome

Pregnancy outcome	Total (n cases with available information)		Clinical trials (n cases with available information)		Post-marketing (n cases with available information)	
	Time from intake to miscarriage	GA at the time of miscarriage	Time from intake to miscarriage	GA at the time of miscarriage	Time from intake to miscarriage	GA at the time of miscarriage
Total spontaneous abortion & missed abortion	36 days (26)	49 days (26)	33 days (19)	48 days (19)	41 days (11)	44 days (9)
Spontaneous abortion	*36 days (22)*	*49 days (22)*	*32 days (17)*	*48 days (17)*	*41 days (9)*	*44 days (7)*
Missed abortion identified at time of induced abortion	*37 days (4)*	*49 days (4)*	*39.5 days (2)*	*49.5 days (2)*	*35 days (2)*	*48 days (2)*

The MAH concluded that based on the available data, the risk of miscarriage does not appear to be increased versus the general population expected risk. This is true both for exposure to UPA during early pregnancy, and for exposure during the cycle of conception.

3.4 Consistent with the non-clinical data, there is no evidence of increased risk of malformations due to exposure to ulipristal acetate during early pregnancy or during the cycle of conception

Among the total pregnancies with reported outcome, there have been 54 live births, 232 induced abortions and 37 ongoing pregnancies (see Table 32). Of these, 190 pregnancies have resulted in either healthy newborns (n=53 babies including two sets of twins), or normal-appearing embryos/foetuses documented on ultrasound at the time of induced abortion (n=134) or during prenatal follow-up of ongoing cases (n=5). The MAH also submitted detailed narratives of these cases.

Three newborns and three foetuses were reported with abnormalities or neonatal complications, none of which were assessed as likely related to UPA exposure.

- One apparently healthy newborn was diagnosed with optic nerve atrophy; this case was reviewed by an Independent Review Board and found unlikely to be related to UPA exposure. One newborn was diagnosed with Beckwith-Wiedemann syndrome; a causal relationship between the reaction and ellaOne could not be formally excluded; however, no similar reports were received and considering the available data, no medical conclusion can be drawn. One case of hypoxic encephalopathy (with epidural and parenchymal haematomas) associated with a traumatic delivery was reported during a study conducted in Hong Kong but neonatal distress appeared to be the cause of the reported symptoms; therefore a causal role of ellaOne was considered as unlikely.
- The three foetal abnormalities included trisomy 21 in a 42-year-old woman who was already pregnant at the time she took ellaOne, a foetal cardiac defect discovered at 12 weeks of pregnancy by ultrasound examination for which very limited information is available and a case of diaphragmatic aplasia and cardiopathy of the foetus for which no medical conclusion could be drawn on an ellaOne causal role, based on the provided data.

Five babies were born after a confirmed pre-existing pregnancy was exposed to UPA at the time of EC intake, all five babies were healthy and delivered uneventfully at term (mean GA at birth of 37.5 weeks).
The reported proportion of malformations (1.4%) is below the established rate observed in the general population (3%) (WHO, 2012).
Growth and development of reported exposed pregnancies lie within the normal range. For the 54 pregnancies resulting in live birth, deliveries occurred at an average of 36.5 weeks gestation; two births occurred earlier than 36 weeks gestation; in one case, the newborn left after a short hospital stay in good health; the other case is the neonate with Beckwith-Wiedemann syndrome (delivery at 31 weeks +2 days). Induced abortions reported after UPA intake demonstrated normal growth and development until an average gestational age of 50 days, 40 days after drug intake, with the exception of the six pregnancies which were diagnosed as missed abortions (see Table 32). Finally, for induced abortions with confirmed established pre-existing pregnancies (n=38) at the time of exposure, 94% were confirmed to be growing and developing normally at the time of induced abortion, at a mean GA of 50 days.
Based on these data, there is no sign of increased risk of malformations due to UPA exposure during early pregnancy or during the cycle of conception, consistent with the non-clinical data.

The MAH concluded that thorough analysis of the available clinical data confirms that there is no evidence of adverse effects of ellaOne exposure on pregnancy maintenance, or on the development of the embryo/foetus, regardless of whether pregnancy pre-existed ellaOne intake:

- The risk of miscarriage is not increased after exposure to UPA during early pregnancy or during the cycle of conception. Miscarriages occur well after drug intake (mean delay of 36 days) and therefore are unlikely to be precipitated by drug exposure.
- There is no evidence of increased risk of malformations due to exposure to UPA during early pregnancy or during the cycle of conception, which is consistent with observations from non-clinical studies.
- Pregnancy course (duration, delivery, complications) does not appear to be modified by the intake of UPA during the cycle of conception or in very early pregnancy.

4 Widening access to the non-prescription setting is likely to decrease the time from UPI to ellaOne intake, and pharmacists play a significant role in verifying that EC is correctly used with regards to time from intercourse

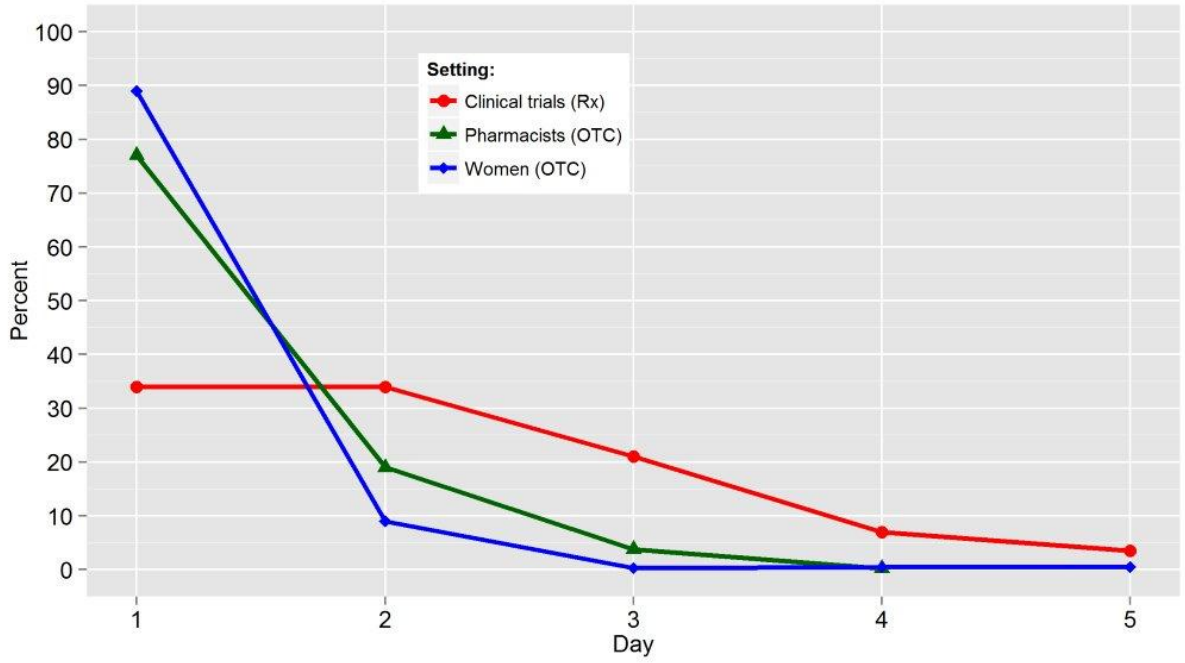
4.1 Widening access to ellaOne through transition to a non-prescription setting will not increase time from UPI to EC intake; it is likely to decrease it

Women use EC promptly after unprotected intercourse (UPI). Multiple studies demonstrate that pharmacy access to EC enhances rapid intake, rather than delay it (Raymond 2006, Ekstrand 2008, Black 2008, Rubin 2011). This is probably because in the non-prescription setting women are able to pick up EC from a local pharmacy, without an appointment to get a prescription. The time delay between a decision to use EC and the intake is minimised through non-prescription pharmacy access. This is critical because the earlier EC is taken after UPI, the more likely it can postpone ovulation thereby preventing unintended pregnancy.

Information on the moment of intake collected in the clinical trial is reflective of the normal provision of the drug in a prescription setting in hospitals and family planning centres. In this study information on 1,899 women was collected (HRA2914-513). Information on the moment of EC request of women (n=707) in a non-prescription environment is available from a study amongst Irish pharmacists (IPU 2013). Another source of data comes from a study amongst women who had used EC during the last year (n=370) evaluating the data in countries where EC is mainly dispensed without prescription (UK,

France and Spain, HRA2914-557). The MAH indicated that a clear shift towards shorter delay between UPI and intake/delivery can be observed for the non-prescription setting compared to the prescription setting (Figure 4).

Figure 4: Day of access to emergency contraception since unprotected intercourse, in a prescription setting or in a non-prescription environment



Ninety percent of women indicated that they had taken the EC product within 24 hours, even if the products can be taken up to 3 or 5 days after unprotected intercourse. The fact that the product is registered up to 120 days after UPI does not mean that as a result women will come later to the pharmacy. The proportion of women asking for EC beyond 5 days is likely to be extremely low, given that the percentage of requests after 72 hours is already less than 3% (see Table 25).

Table 25: Percentage of women asking for emergency contraception more than 72 hours after unprotected intercourse

Country (source of data), n of women surveyed	***% women asking for EC more than 72 hours after UPI***
France (HRA2914-557), n=150	2%
Ireland (IPU 2013), n=707	0.2%
Spain (HRA2914-557), n=112	3%
UK (HRA2914-557), n=108	1%

The CHMP provided additional information on the cited studies.

Ekstrand et al., 2008 randomized girls aged 15-19 years to an intervention group (IG) or control group (CG). Both groups received ECP on request. The intervention group received one extra dose of ECP, condoms and an information leaflet regarding ECP and condom use. At the 3-month follow-up, the intervention group had used ECP sooner after UPI than the control group (mean time IG: 14 h, CG: 25 h).

Black et al. 2008 compared access through pharmacies with clinical services. Seventy percent of women who went to a pharmacy and 44% who went to a clinical service obtained EC within 24 hours.

In study HRA2914-557 also two other countries were taken into account in which levonorgestrel-EC has a prescription status, i.e. Germany and Italy (see Table 26). In Germany 68 subjects were surveyed and in Italy 70 subjects. The data of this study suggest that the prescription status does not impact the percentage of women that takes emergency contraception within 24 hours, with 83% in Germany ranging to 92% in Spain. In Spain, however, where emergency contraception has a non-prescription status the highest percentage of women taken emergency contraception within 12 hours is observed, i.e. 63%. Further, as can be seen in the table below, the prescription status does not affect the percentage of women with intake after 48 hours. In all surveyed countries this percentage is low, varying from 1 to 5%.

Table 26: Time to intake of Emergency Contraception

- *How long after the unprotected sexual intercourse did you take emergency contraception?*

	Germany	UK	Italy	France	Spain	TOTAL
	N = 68	N = 108	N = 70	N = 150	N = 112	
Less than 12 hours / during the following half day	40%	42%	40%	40%	63%	45%
Between 12 and 24 hours / during the following day	43%	45%	46%	48%	29%	42%
Between 25 and 48 hours / in the following two days	12%	12%	13%	9%	5%	10%
Between 49 and 72 hours / in the following three days	4%	-	-	1%	-	1%
Between 73 and 120 hours / in the following five days	-	1%	-	1%	1%	1%
More than 120 hours / more than five days after	1%		1%	1%	2%	1%

4.2 Few women request EC beyond 5 days after UPI – and pharmacists are well trained to ask when UPI happened before they provide EC

Even when the proportion of women requesting EC after more than 5 days is extremely low, the chances that these women will obtain EC (ellaOne) are even lower. This is because pharmacists are well trained to deliver EC. In an evaluation of pharmacists' behaviour (110 pharmacists from 9 European countries where EC can be accessed in pharmacy without prescription, HRA2914-556), 84% confirmed that they *always* ask questions when dispensing EC. This increased to 100% with those asking questions *often*. The most frequently asked question prior to dispensing EC was: "*How many days have passed since the unprotected intercourse?*" (88%).

Finally, the proposed PI, especially the front face of the outer carton, emphasises the need for a rapid intake to maximise effectiveness.

The MAH believes that the transition of ellaOne to non-prescription status will decrease the time delay between UPI and the moment of ellaOne intake, and that pharmacists will continue to ask about the time since UPI. Hence, real life is likely not to substantiate the concern that 'widening access to the non-prescription setting might increase the potential for late usage and enhance the possibility that a woman is already pregnant when exposed to UPA'.

5 A contraindication for intake during pregnancy is not justified for safety reasons nor required in accordance with the relevant guidelines. Appropriate warnings about intake during pregnancy are included in the SmPC and package leaflet.

The MAH considers that a contraindication in pregnancy is not justified:

- The non-clinical data generated using the most rigorous scientific methodology and constituting the most stringent assessment of potential toxicity show that UPA intake for EC is not associated with any risk of teratogenicity.
- Thorough analysis of clinical data does not show an increased risk for miscarriage nor major malformations in comparison to the rate in the general population.
- In accordance with the CHMP *Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling* (EMEA/CHMP/203927/2005) and with the Guideline on SmPC, the MAH considers that given the absence of a signal from both preclinical and clinical data a contraindication for pregnancy is not justified.

However, the proposed Product Information for ellaOne gives clear information and recommendations on use in pregnancy, especially the two following messages:

- pregnancy should be ruled out before ellaOne intake if a woman's menstrual period is late (SmPC section 4.2)
- ellaOne is not intended to be used and does not work if already pregnant (SmPC section 4.6).

The MAH concluded that non-clinical and clinical data indicate a lack of evidence that ellaOne is teratogenic or increases the risk of adverse pregnancy outcomes.
The non-clinical studies with UPA, which were performed in validated animal models have not evidenced any adverse effect on the offspring. The data from clinical trials, post-marketing studies and pharmacovigilance provide information on 568 pregnancies where intake happened during the cycle of conception. These data have been assessed methodically and thoroughly. No safety signals have been detected and considering all these sources it can be concluded that adverse effects on pregnancy are not to be expected. A contraindication for intake during pregnancy is therefore considered neither to be appropriate nor in accordance with the relevant guidelines.
Although it could be thought that widening access to the non-prescription setting might increase the potential for late usage and enhance the possibility that a woman is already pregnant when exposed to UPA, the transition of ellaOne to non-prescription status will result in earlier use of the product compared to the prescription status. Earlier intake means a greater chance of use before ovulation thereby greater chance of preventing unwanted pregnancy. Pharmacists are used to ask women requesting emergency contraception about the time delay since the unprotected intercourse and will continue to do so. The PI and especially the front of the outer carton of ellaOne state that intake should happen as soon as possible after unprotected intercourse.
Whereas the benefit of faster access to ellaOne is evidence-based, the risk remains hypothetical and not supported by evidence. The pregnancy rate has been shown to be the lowest when taken within the first 24 hours (Glasier 2010), and pharmacodynamic data have confirmed the importance of intake within the shortest time so that it can take place before it can postpone ovulation (Brache 2013). Because the non-prescription status of ellaOne would provide more rapid access to a more efficacious emergency contraceptive product, the MAH considers that any hypothetical risks are considered minor in view of the well-documented public health risks and adverse health outcomes associated with unintended pregnancy.
The MAH further considers that rapid access to a more efficacious emergency contraceptive product will be to the advantage of women trying to prevent unwanted pregnancy and that all criteria of the EC Guideline on changing the classification for the supply of a medicinal product for human use are met.

Overview of data sources

Data obtained come from three distinct sources; clinical trials of ellaOne, a retrospective record review of drug use at family planning clinics in Oregon, and the company's pharmacovigilance database. Data are presented starting from the most robust data source.

Table 27: Sources of data of all pregnancies reported after intake of UPA

Source of data	Total pregnancies	
	All	With known outcome
Clinical trials	94	83
Retrospective study, Oregon	55	39
Pharmacovigilance	419	227
Total	**568**	**349**

Table 28: Sources of data of pregnancies reported after intake of UPA that ended in elective induced abortion

Source of data	Total elective induced abortions	Cases of induced abortion further assessed	
		Cases with supplemental information received	Cases with pregnancy growth / development assessed
Clinical trials	58	58	55
Retrospective study, Oregon	33	33	33
Pharmacovigilance	121*	69	46
Total	**212**	**160**	**134**

*including the initial 78 cases

Pregnancy growth and development assessment

The presence of an intrauterine pregnancy is generally documented by an ultrasound (US) at the time of abortion, if not at the time of pregnancy diagnosis. US allows for an accurate determination of gestational age (GA, in combination with last menstrual period date, serial beta-hCG levels and coital history). The viability of a pregnancy can also be assessed based on a visible foetal heartbeat after 6-7 weeks GA and the observation of expected size and morphology for GA. Finally the viability can also be assessed by comparing the growth of a gestational sac and an embryo between two US examinations. An overall assessment of the development of the embryo or foetus, and of the gestational sac is routine practice. Pathology examination is seldom performed in the setting of elective induced abortion and when available, is not informative about the actual pregnancy viability. The role of pathology examination in this setting is to confirm the completeness of abortion although this can be achieved by routine surgical procedure.

Pregnancies in clinical trials of ellaOne

Cases of pregnancy recorded during prospective phase II and III clinical trials in the development of UPA for EC represent the highest quality source of data on exposure; systematic pregnancy tests were performed on admission to clinical trials, and were repeated after the index cycle in which unprotected intercourse occurred and EC was taken, loss to follow-up of reported cases was minimal, and pre-treatment pregnancies were clearly identified by serum beta-hCG measurement at the time of intake.

Pregnancy cases collected during ellaOne development clinical trials are presented in the table below.

Table 29: Pregnancy cases collected during ellaOne development clinical trials

Pregnancy outcome	Number of trial pregnancy cases		
	Total	Timing of exposure	
		Before conception	1st trimester
Lost to follow-up / Unknown outcome	11	10	1
Ongoing	0	-	-
Ectopic pregnancy	0	-	-
Spontaneous miscarriage	17	14	3
Elective termination	58	51	7
Live birth	8*	7	1
Total	94	83	11

*8 births, 9 babies (1 twin pregnancy was exposed to 20 mg a day for 10 days during the first trimester

Pregnancies from the retrospective study, Oregon (HRA2914-648)

In this study, data come from pregnancies diagnosed after ellaOne intake in routine use at clinics that provide both contraception and abortion services (affiliated with Planned Parenthood Federation of America) in the U.S. state of Oregon. A retrospective chart review and analysis was performed in an effort to describe the outcome of these pregnancies using data from the medical records. The MAH has conducted this retrospective record study in all 10 family planning clinics affiliated to the Planned Parenthood Federation of America (PPFA) in Oregon, because the frequency of ellaOne prescription is high (more than 50,000 units in 2012) and therefore the chances of identifying cases of exposed pregnancies or treatment failure are great. Furthermore, the electronic database capture in this group of family planning clinics allowed to crosslink a prescription of ellaOne to a positive pregnancy test or an induced abortion for a given patient within a specific timeframe compatible with exposure during the cycle of conception. After IRB approval of the study, a search was performed in the electronic database system to retrieve all cases where a positive pregnancy test was recorded within two months or an abortion was sought within three months following a prescription of ellaOne. From this study, information is available on 55 pregnancies (Table 30).

Table 30: Status and outcome of all pregnancies diagnosed after ellaOne intake in Oregon clinics since ellaOne launch in USA (from Dec 2010 to Aug 2013) (updated with follow-up information in Aug 2014)

Pregnancy outcome	Total	Timing of exposure during cycle of conception		
		Intake before pregnancy	Intake while already pregnant	Unknown status of pregnancy at intake
Ongoing	9	0	0	9
Healthy live birth	1	-	1	-
Ectopic pregnancy	1	0	0	1
Spontaneous miscarriage	2	2	1*	0
Induced abortion total	35	9	20	6
normal appearing pregnancy†	33	8	19	6
missed abortion	1	-	1	-
unknown	1	1	-	-

Unknown outcome	7	0	0	7
Total	55	10	21	25

* one patient took ellaOne twice, once before conception and once 18 days after conception
† according to ultrasound appearance and gestational and last menstrual period date

Pregnancies reported in post-marketing pharmacovigilance

Pregnancy cases in pharmacovigilance (PV) are coming either from solicited sources (observational studies such as study HRA2914-515, pregnancy registry) or spontaneously reported (through health care professionals, authorities or consumers). These cases include both prospective (pregnancy diagnosed but outcome yet unknown at time of initial report) and retrospective (pregnancy outcome already occurred at the time of initial report but may be further documented by active follow-up) case reports. The summary of all these PV pregnancy cases is detailed in the following table.

Table 31: Status and outcome of all pregnancies reported to pharmacovigilance after UPA intake in the cycle of conception during the post-market period (data-lock point 31/08/2014)

Pregnancy outcome	**Total**	**Timing of exposure during cycle of conception**		
		Intake before conception	Intake while already pregnant	Pregnancy status unclear at intake
Unknown outcome	169	46	14	109
Ongoing	28	10	2	16
Live births Uneventful pregnancy with healthy baby Complications	45 43 2	28 28 β -	3 3 -	14 12 2
Ectopic pregnancy	9	5	0	4
Spontaneous miscarriage	29	13	1	15
Induced abortion	139	77	11	51
Total	419	181	31	207

* total number of pregnancies is 45, and number of babies is 47 β one twin pregnancy with two healthy babies

Finally, all pregnancy cases were compiled in the following summary table which was submitted in September 2014 (Table 32) and assessed for status of pregnancy at the time of intake according to available data and in a harmonized way for all post-marketing data.

Table 32: Status and outcome of all pregnancies diagnosed after UPA intake in the cycle of conception from development trials to post-market period (data-lock point 31/08/2014) (updated with follow-up information in November 2014)

Pregnancy outcome	Total	Time of exposure during cycle of conception		
		Intake before pregnancy	Confirmed pre-existing pregnancy at intake	Pregnancy status unclear at intake
Ongoing	37	10	2	25
Normal appearing pregnancy during pre-natal care	*5*	*3*	*1*	*1*
Unknown	*32*	*7*	*1*	*24*
Live birth	54[¶]	35	5	14
Uneventful pregnancy with healthy baby(ies)	*51*	*34[β]*	*5[β]*	*12*
Complications	*3*	*1**	-	*2***
Ectopic pregnancy	10	5	0	5
Miscarriage	48	29	4	15
Induced abortion, Total	232	137	38	57
Normal- appearing pregnancy	*134*	*83*	*31*	*20*
Foetal defect	*3*	*0*	*1°*	*2[♦ Ψ]*
Missed abortion[†]	*6*	*3*	*1*	*2*
Unknown	*89*	*51*	*5*	*33*
Unknown outcome	187	56	15	116
Total	568	260	64	244

[¶] total number of pregnancies is 54, and number of babies is 56
[β] one twin pregnancy with two healthy babies
*one case of congenital optic nerve atrophy at birth, unrelated to ellaOne intake
** one delivery complication associated with fetal neonatal distress, unrelated to ellaOne intake; one case of Beckwith-Wiedemann syndrome for which available information is insufficient to formally exclude a causal relationship with ellaOne intake
[Ψ] one case of fetus with diaphragmatic aplasia and cardiopathy leading to therapeutic abortion at 22 weeks of pregnancy, for which available information is insufficient to assess the relatedness with ellaOne intake
° foetus with trisomy 21, unrelated to ellaOne intake
[♦] cardiac defect, available information too limited to assess relatedness to ellaOne intake
[†] abnormally growing or anembryonic pregnancies, causal relationship to ellaOne intake not assessable

Results

Clinical trial pregnancies

From the 58 cases of induced abortion examined from clinical trial data, information allowing an assessment of the development of the pregnancy up until time of induced abortion is available in 55 cases. Pathology examination results have been made available for two cases for which no abnormal findings were observed.

In 53 cases, pregnancies appeared to grow and develop normally for a mean of 37 days following intake (corresponding to a mean GA of 48 days/ 7 weeks). In two cases, the US results allowed the identification of a missed abortion, corresponding to a pregnancy that had stopped growing normally

at the time of induced abortion and that would have subsequently led to spontaneous abortion. These missed abortions were identified at 31 and 48 days following intake (corresponding to a mean GA of 35 days/ 5 weeks and 42 days/ 6 weeks, respectively). Both occurred more than 30 days after intake, so a link with treatment intake is unlikely. Results of pregnancy cases diagnosed after intake of 10 mg UPA are similar to those observed with the whole sample of induced abortion cases.

Table 33: Time elapsed between intake and induced abortion for clinical trial cases

Pregnancy outcome	Time (days) elapsed between intake and outcome Mean (min;max) (total number of cases)		
	All cases	All cases, excluding 10mg single dose	10mg single dose
Induced abortion	37 (7;73) (58)	37 (7;73) (42)	40 (17;70) (16)
normal appearing pregnancy	37 (7;73) (53)	36 (7;73) (37)	40 (17;70) (16)
missed abortion	40 (31;48) (2)	40 (31;48) (2)	- (0)
unknown	44 (26;70) (3)	44 (26;70) (3)	- (0)

Table 34: Gestational age at time of induced abortion for clinical trial cases

Pregnancy outcome	Gestational age (days) at outcome Mean (min;max) (total number of cases)		
	All cases	All cases, excluding 10mg single dose	10mg single dose
Induced abortion	47 (14;97) (58)	46 (14;97) (42)	51 (35;79) (16)
normal appearing pregnancy	48 (14;79)* (53)	46 (14;70)* (37)	51 (35;79)* (16)
missed abortion	39 (35;42)* (2)	39 (35;42)* (2)	- (0)
unknown	69 (48;97)** (3)	69 (48;97)** (3)	- (0)

*estimated using U/S data
**estimated using LMP

In the three cases for which pregnancy growth could not be examined, induced abortion took place a mean of 44 days after intake (corresponding to a mean GA of 69 days/ 10 weeks according to LMP date). This mean time interval of 44 days is indicative that any adverse effects on pregnancy due to ellaOne would be unlikely.

Pregnancies from the retrospective study, Oregon

From all 33 cases of induced abortion from the study in Oregon, information is available for an assessment of the development of the pregnancy up until time of induced abortion. None of the subjects had a pathology examination of the products of conception following abortion.

In 32 cases, pregnancies appeared to grow and develop normally at a mean of 40 days following intake (corresponding to a mean GA of 55 days/ 8 weeks). The 33rd subject had an anembryonic pregnancy corresponding to a missed abortion. The size of the gestational sac on US was consistent with 43 days gestation (6 weeks), but no foetal pole was identifiable. She was diagnosed with an early pregnancy failure and she underwent medical abortion which she completed without complication. The missed abortion occurred 31 days after intake, so a link with treatment intake is unlikely.

Table 35: Time elapsed between intake and induced abortion for pregnancies reported in the retrospective study, Oregon

Pregnancy outcome	Total N (n with time available)	Time (days) elapsed between intake and outcome Mean (min;max)
Induced abortion	33 (26)	39 (12;77)
normal appearing pregnancy	32 (25)	40 (12;77)
missed abortion	1	31

Table 36: Gestational age at outcome for pregnancies reported in the retrospective study, Oregon

Pregnancy outcome	Total N (n with GA available)	Gestational age (days) at outcome Mean (min;max)
Induced abortion	33 (26)	55 (38;86)
normal appearing pregnancy	32 (25*)	55 (38;86)
missed abortion	1*	43

*estimated using U/S data

Pregnancies from spontaneous reports to pharmacovigilance

From the 121 cases of induced abortion reported spontaneously in pharmacovigilance, supplemental information was received for 69 cases for which 27 US reports have been made available. In total, pregnancy growth and development up until time of induced abortion could be assessed in 46 cases according to LMP date, GA at the time of outcome, presence of a heartbeat on US, global appearance on US and reporter's opinion. In 75 cases, no data were made available to allow an evaluation of the pregnancy growth and development. For three cases, a pathology examination report of the products of conception following abortion was also received for which no abnormal findings were observed.

In 44 cases, pregnancies appeared to grow and develop normally for a mean of 50 days following intake (corresponding to a mean GA of 50 days/ 7 weeks) (Table 37 and Table 38). In one case, the viability of the pregnancy at US was uncertain 39 days following intake (corresponding to a GA of 52 days/ 7.5 weeks). Because missed abortion occurred 39 days after intake, it is unlikely it is causally linked to treatment intake. In a second case, pregnancy was anembryonic corresponding to a missed abortion but no further information could be obtained.

Table 37: Time elapsed between intake and induced abortion for pregnancies reported in pharmacovigilance since launch (until 31 August 2013)

Pregnancy outcome	Total N (n with time available)	Time (days) elapsed between intake and outcome Mean (min;max)
Induced abortion	121 (58)	43 (14;110)
normal appearing pregnancy	44 (23)	50 (14;110)
missed abortion	2 (1)	39
unknown	75 (34)	39 (14;100)

Table 38: Gestational age at time of induced abortion for pregnancies reported in pharmacovigilance since launch (until 31 August 2013)

Pregnancy outcome	Total N (n with GA available)	Gestational age (days) at outcome Mean (min;max)
Induced abortion	121 (62)	52 (23;104)
normal appearing pregnancy	44 (23*)	50 (23;97)
missed abortion	2 (1*)	52
unknown	75 (38**)	53 (33;104)

*estimated using the earliest U/S available (pregnancy diagnosis or time of induced abortion)
**estimated using LMP

In the 75 cases for which pregnancy growth could not be examined, induced abortion took place a mean of 39 days after intake (corresponding to a mean GA of 53 days/ 7.5 weeks according to LMP date). This mean time interval of 39 days is indicative that any adverse effects on pregnancy due to ellaOne would be unlikely.

Table 39: Time elapsed between intake and induced abortion for all cases

Pregnancy outcome	Total N (n with time available)	Time (days) elapsed between intake and outcome Mean (min;max)
Induced abortion	212 (142)	40 (7;110)
normal appearing pregnancy	129 (101)	41 (7;110)
missed abortion	5 (4)	38 (31;48)
unknown	78 (37)	39 (14;100)

Table 40: Gestational age of pregnancies at the time of induced abortion for all cases

Pregnancy outcome	Total N (n with GA available)	Gestational age (days) at outcome Mean (min;max)
Induced abortion	212 (146)	53 (23;104)
normal appearing pregnancy	129 (101*)	49 (14;97)
missed abortion	5 (4*)	43 (35;52)
unknown	78 (41**)	54 (33;104)

*estimated using the earliest U/S available (pregnancy diagnosis or time of induced abortion)
**estimated using LMP

In five cases, the pregnancy was non-viable and would have subsequently led to spontaneous abortion. In the four cases for which information is available, missed abortion was identified a mean of 38 days following intake (corresponding to a mean GA of 43 days/ 6 weeks). None were identified earlier than 30 days after drug intake. Because missed abortion was identified 38 days after intake, the link with treatment intake is unlikely.

For the remaining 78 cases, only the time interval between drug intake and abortion, and an estimation of GA based on LMP, are available, without any further data having been reported to allow evaluation of pregnancy growth and development. In these cases, induced abortion took place a mean of 39 days after intake (corresponding to a mean GA of 54 days/ 7.7 weeks according to LMP date). This mean time interval of 39 days is indicative that any adverse effects on pregnancy due to ellaOne would be unlikely.

Overall, a report of pathology examination of the products of conception following abortion was received for five cases out of 212, and no abnormal findings were observed from the any of the pathology examination results.

A review of the cases of induced abortion has been provided by the MAH. Additional cases have been identified since the previous round of this procedure, and the total now comes to 136 induced abortions with known outcome. Two of these cases involved foetal defects. Of the remaining cases, 5 were missed abortions, and 129 appeared to have grown and developed normally. The data about induced abortions are of limited value, since apart from a small number of cases where a pathology examination was performed, the evaluation of the foetuses is restricted to overall growth and development. Although it is likely that major malformations can be detected in this way, smaller malformation might go unnoticed. However, these data, together with the lack of increased rate of miscarriage contribute to the overall dataset.

Benefit risk of ellaOne as a non-prescription product in young adolescents and adults as assessed by the MAH

In the second Request for Supplementary Information, the MAH was also asked to discuss the benefit/risk of unrestricted access to ellaOne on a non-prescription basis in young adolescents, as it is proposed that the product is switched with no age restriction and there is a concern about the level of support and advice that would be available for this vulnerable age-group in an unsupervised non-prescription setting.

The MAH provided the following assessment of the benefit/risk of unrestricted access to ellaOne on a non-prescription basis in young adolescents.

1. The benefit risk assessment of unrestricted access to ellaOne on a non-prescription basis is favourable in women of all ages, and there is no scientific reason to impose an age restriction in the MA of ellaOne.

1.1 *Avoiding unintended teen pregnancy, through provision of emergency contraception, has the potential to benefit young women, their children, as well as health and social care systems. While all women should have the option to promptly access to the most effective method of EC, arguably adolescents have the most to gain from preventing unintended pregnancy.*

Teen mothers and their children face poorer prospects in life than do women who delay motherhood until later in life. There are health risks for the baby and children born to teen mothers are more likely to suffer health, social, and emotional problems than children born to adult mothers. Teen mothers are also more likely than other young women of their age to drop out of school, live in poverty and rely on public assistance (Coley 1998, Francesconi 2007, Fletcher 2012). Teen pregnancies are generally unintended and in many cases, adolescents choose to terminate their pregnancy. Teen pregnancy is a recognised public health concern.
EC is the only option to attempt to prevent an unintended pregnancy after unprotected intercourse (UPI); as such, it constitutes an important tool in the range of contraceptive options that reduce the risk of unintended pregnancy. Adolescents are the least likely group of women to be using effective contraception consistently, making EC an especially important tool for them. Indeed adolescents have specific challenges of starting regular contraception, and condom failures are particularly frequent at the time of sexual debut (Davtyan 2000).

Because EC should be used as soon as possible after UPI, levonorgestrel (LNG) EC has been made available in a non-prescription setting in 23 countries of the EEA. As a result, adolescents go directly to the pharmacy when they need EC. In a few countries across Europe, there is an age restriction for girls under 15 or 16 years who then need a prescription to access LNG EC. In practice, pharmacists see very few girls under 16 coming for EC. In a survey carried out in 2013 in the UK on women presenting to a community pharmacy with a request for EC, out of the 211 respondents overall, 3 were aged less than 16 years: one aged 14 and 2 aged 15 years (Michie 2013, accepted for publication, personal communication with the authors).

Because EC should be used as soon as possible after UPI, levonorgestrel (LNG) EC has been made available in a non-prescription setting in 23 countries of the EEA. As a result, adolescents go directly to the pharmacy when they need EC. In a few countries across Europe, there is an age restriction for girls under 15 or 16 years who then need a prescription to access LNG EC. In practice, pharmacists see very few girls under 16 coming for EC. Rapid access in pharmacy is relevant for both LNG and ellaOne, but ellaOne is more effective at preventing pregnancy than LNG. Making ellaOne directly accessible in pharmacy would mean more adolescents could benefit from this more effective option and they could take it sooner after the episode of UPI. For this population in whom the impact of unintended pregnancy is arguably highest, it is of crucial importance. While all women should have the option to have better access to the more effective method of EC, arguably adolescents have the most to gain from preventing an unintended pregnancy.

1.1. There is no evidence of an increased risk profile in adolescents compared to adult women

1.1.1. Safety profile of ellaOne in adolescents is similar to adult women

The study HRA2914-515 in postmenarcheal adolescents shows that the safety profile for ellaOne is similar when compared to adult women.

Table 41: Incidence and relative risk [95% CI] between age classes for most frequent adverse events and events of interest – safety population

	Total (N=472)	**< 18 years old (N=239)**	**RR[(a)] [95%CI] compared to ≥18 years old**	**< 16 years old (N=64)**	**RR[(a)] [95%CI] compared to ≥16 years old**
Most frequent adverse events					
Headache	51 (10.8%)	28 (11.7%)	1.18 [0.70;1.99]	9 (14.1%)	1.43 [0.73;2.78]
Nausea	30 (6.4%)	12 (5.0%)	0.66 [0.32;1.34]	1 (1.6%)	0.32 [0.04;2.34]
Abdominal pain	16 (3.4%)	5 (2.1%)	0.47 [0.16;1.32]	2 (3.1%)	1.10 [0.26;4.72]
Upper abdominal pain	15 (3.2%)	9 (3.8%)	1.42 [0.52;3.94]	5 (7.8%)	**3.34 [1.18;9.45]**
Events of interest					
Change in length of treatment cycle > 7 days	142 (37.0%)	84 (42.6%)	**1.36 [1.04;1.78]**	23 (42.6%)	1.18 [0.84;1.66]
Menorrhagia	140 (29.7%)	54 (22.6%)	**0.61 [0.46;0.82]**	14 (21.9%)	0.73 [0.45;1.19]
Metrorrhagia	99 (21.0%)	51 (21.3%)	1.04 [0.73;1.47]	13 (20.3%)	0.99 [0.59;1.67]
Dysmenorrhea	9 (1.9%)	5 (2.1%)	1.19 [0.32;4.38]	1 (1.6%)	1.13 [0.14;8.85]

(a) RR = relative risk

Results are expressed as n (%) women who experienced at least once the event.

For change in cycle length, percentages are calculated on the number of women with available data on usual cycle length and length of treatment cycle (n=384 for total population, n=197 for women<18 years old and n=54 for women <16 years old).

Considering the expected small incidence of events, relative risk was corrected by adding 0.5 to the number of women presenting the event in each class.

1.1.2. Efficacy of ellaOne in adolescents shows the pregnancy rate is similar to adult women

The study HRA2914-515 in postmenarcheal adolescents shows that the pregnancy rate for ellaOne is similar when compared to adult women.

A pregnancy was reported for seven women (1.5%) out of the 464 women for whom pregnancy status was available, including two between 16 and 18 years old. None of these women were pregnant at the

time of UPA intake. Only one pregnancy (which occurred in a 20-year old woman with a subsequent healthy birth at 38 weeks) was considered compatible with EC failure according to the investigator.

1.1.3. Multiple studies have shown that sexual risk behaviour of adolescents is not influenced by access to emergency contraception

Efforts to facilitate access to EC for adolescents have been challenged by concerns that they may result in increased unprotected intercourse, higher rates of pregnancy and STIs. Several studies have examined these concerns.

The data provided from a study published in 2004 (Walker DM) in Mexico showed an increase in condom use among adolescents who have used EC.

A study performed in 2005 (Raine 2005) followed up 2,117 adolescents and young adults including 964 adolescents (90 of whom were aged younger than 16 years) during a mean period of 6.9 months to compare the sexual behaviour of a group who had direct access to EC through pharmacies and advance provision compared to a control group (who had clinical access to EC). No detrimental effect on contraceptive use or sexual behaviour was shown in the pharmacies or advance provision groups compared with the control (Raine 2005). An age-stratified analysis performed on these data shows that girls below 16 years behaved no differently in response to increased access to EC from the other age groups (Harper 2005). Behaviours of adolescents did not differ with increased access to EC, including: UPI at follow-up, condom use, STI acquisition or pregnancy. Additionally, adolescents with increased access to EC did not become more vulnerable to unwanted sexual activity (Harper 2005).

Other studies looking at situations when EC is provided in advance of need, known as advance provision, to adolescents are also informative. Several studies showed that advance provision of EC does not negatively impact ongoing contraceptive use or sexual risk-taking behaviours, such as UPI or condom use. In addition, the acquisition of STIs does not increase with advance provision of EC (Gold 1997, Raymond 2006, Ekstrand 2008).

1.2. Through pharmacy provision, appropriate advice and support can be offered to adolescents

The number of adolescents under 16 requesting EC from pharmacy is very small, but direct and rapid pharmacy access is valued by the adolescents recognising they need EC. In a study in adolescents who obtained EC directly in pharmacy in the Washington state (USA), 22% said they would wait to see if they got pregnant rather than seek out EC if the pharmacy service were not available and 20% did not know what they would have done (Sucato 2001).

Providing adolescents with adequate support and advice at time of EC provision is an opportunity to spread important individual and public health messages, which is of particular importance in the absence of prior visit to a doctor, such as regular contraceptive measures, the prevention of STIs or the protection of vulnerable population (i.e. non-volitional sex).

The MAH worked with some organisations from different countries on pharmacy best practice to deal with requests for EC coming from adolescents in accordance with national requirements.

The MAH intends to provide pharmacists with appropriate materials that could help them address EC requests coming from adolescents, in line with the existing pharmacy best practice. For example, materials will encourage pharmacists to ensure that women attending pharmacies for EC have access to a regular contraceptive method, which they can start as soon as possible. The MAH is also willing to take into consideration any national requirements when applicable.

The MAH is also committed to dialogue with national pharmacy organisations particularly on ‘the role of the pharmacists when dispensing EC to young adolescents’. How the MAH could best support the pharmacy profession in this regard will be discussed with these organisations.

In conclusion, the MAH considers that the benefit risk assessment of unrestricted access to ellaOne on a non-prescription basis in adolescents is favourable and there is no scientific reason to stipulate an age restriction in the community MA of ellaOne.

Discussion by the CHMP about the third criterion

Article 71 of Directive 2001/83/EC and the Guideline on changing the classification for the supply of a medicinal product foresees that medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side-effects of which require further investigation.

The CHMP agrees with the MAH's points that the pharmacological activity and side effects of ellaOne have been characterized, and no significant safety findings have been identified.
The safety of ellaOne has been investigated in the studies submitted at time of the initial marketing authorisation. These data are now extended by a study on repeated administration (HRA2914-554; every 5 days and every 7 days) and a study in adolescents (HRA2914-515). The data of these studies confirm the positive benefit/risk ratio of ellaOne.

Moreover, the CHMP considers the MAH has provided sufficient reassurance on lack of negative effects to the foetus after uterine exposure to ulipristal (including teratogenicity) based on the updated non-clinical and clinical data now available as described in the following paragraphs:

Non-clinical data on teratogenicity
The MAH has reviewed the available data on reproduction toxicity, in light of possible teratogenic effects of ulipristal. It is stated that there is no evidence of a teratogenic effect in rats, rabbits, and monkeys. This is agreed. However, the doses used are low. The MAH uses a conversion factor to extrapolate between animal data and humans based on mg/m2. Although this is agreed when no toxicokinetic data are available, at the time of registration it was concluded that based on the available limited toxicokinetic data, the exposures achieved in the reproduction studies are likely below or at clinical exposures. Due to the pharmacological effect of UPA, this cannot be further explored in non-clinical studies, and definitive proof of lack of teratogenic potential should come from clinical data.

In conclusion, available animal data, likely at or below clinical exposure, do not indicate a teratogenic potential.

Non-clinical data on embryolethality
No human studies have been conducted on the possibility of using ulipristal acetate as an abortifacient. It is therefore unknown whether ulipristal acetate might induce pregnancy loss, and if so, at what dose. The potential to induce termination of pregnancy was evaluated in guinea pigs and macaque monkeys. In both studies termination of pregnancy was achieved both in early pregnancy (monkeys) and late pregnancy (guinea pigs). The MAH argues that doses are high, based on comparison of mg/m2 conversion. Since no toxicokinetic data are available for either species, this method of comparing doses could be acceptable, although data from another monkey species indicate that exposure is lower than expected from the conversion based on mg/m2. However, comparison to mifepristone with known abortifacient potential is possible since both studies used mifepristone as a comparator. In guinea pigs, ulipristal seems somewhat less potent as mifepristone, whereas no meaningful differences in potential between the two compounds were evident in monkeys. Based on extrapolations from these non-clinical data, it may be concluded that ulipristal acetate is far less potent compared to mifepristone. Since the dose needed to induce abortion in humans is at least 200 mg for mifepristone (albeit only in combination with a prostaglandin analogue), it is extremely unlikely that a single tablet of 30 mg ulipristal will induce an abortion when taken during pregnancy.

In these extrapolations, it has also not been taken into account that in women mifepristone always needs to be taken in combination with a prostaglandin to be effective.

In conclusion, animal data comparing abortifacient potential of ulipristal to mifepristone may indicate that ulipristal is far less potent than mifepristone. Therefore a single tablet of 30 mg ulipristal is extremely unlikely to induce an abortion in humans.

Clinical data

After 3 million doses of ellaOne used, a total of 568 pregnancies following UPA intake have been reported (data-lock point 31 August 2014). In comparison, in the previous round (data-lock point 31 August 2013) a total of 477 pregnancies were reported. Thus, in one year information is collected on an additional 91 pregnancies following UPA intake.

A thorough analysis of all available data brings to light no evidence of adverse effects of ellaOne exposure on pregnancy maintenance or on the development of the embryo/foetus, regardless of whether pregnancy pre-existed intake. The clinical data, although still limited, are reassuring.

The new safety data generated in study HRA2914-648 have reassured that no negative effects were observed for the foetus or the mother, which is related to guideline criterion 3. It was decided based on the pregnancy outcome data available, to which this study contributed 48 pregnancies that ellaOne does not meet this criterion 3.
The available data are sufficient to conclude that the risk of exposure of ellaOne is likely to be low. Further, during the first two weeks after conception, and before the expected date of menses, the developing embryo is not susceptible to teratogenesis.

The number of exposed pregnancies is low, due to the effectiveness of the product in preventing pregnancy, the voluntary basis of reporting a pregnancy, and the fact that many women becoming pregnant have an elective abortion (232 out of 568 pregnancies following UPA intake, 41%).
One can discuss whether the number of exposed pregnancy outcomes currently available, including an additional 91 pregnancies following UPA intake can be considered sufficient evidence of an absence of adverse effects in the foetus after exposure to ulipristal during pregnancy. At least, one can conclude that the data are reassuring in a reasonable number of pregnancies. Consideration should also be given to 1) the low number of exposed pregnancies due to the effectiveness of the product in preventing pregnancy, 2) the voluntary basis of reporting a pregnancy, and 3) the fact that many women becoming pregnant have an elective abortion (232 out of 568 pregnancies following UPA intake, 41%). Information on human pregnancy outcome can also be collected in a non-prescription setting, and the MAH has committed to continue collecting pregnancies having been exposed to ellaOne, and monitoring and documenting the outcome.

Malformations

A total of 191 pregnancies with known foetal or neonatal outcome have been gathered by the MAH (data-lock point 31 August 2014). In comparison, in the previous round information was provided on 163 pregnancies (data-lock point 31 August 2013). These include live births (54) and induced abortions (137). The amount of data should still be viewed as limited, especially since a large percentage concern induced abortions, of which the examination of the foetus is restricted to general growth and development in most cases.
Of the 137 induced abortions, 134 resulted in normal appearing fetuses, and 3 foetal defects (2.2%). These foetal defects were trisomy 21, cardiac defect and diaphragmatic aplasia and cardiopathy. This is below the rate of malformations seen in the general population of 3%, and thus, so far, there are no signs of increased risk of malformations due to exposure to UPA during early pregnancy or in the cycle of conception.

From the 54 live births, complications were reported in 3 live births. These concerned infant optic nerve atrophy, Beckwith-Wiedemann syndrome (BWS) (chromosome 11 mutation) and hypoxic complicated delivery. The relationship with UPA was considered unlikely for infant optic nerve atrophy and hypoxic complicated delivery, this is agreed with. For BWS the MAH indicated that the relationship cannot be formally excluded, but that no similar reports were received. Also, the CHMP considered the relationship for BWS unlikely.

Miscarriage

Among 349 cases of known pregnancy outcome, there were 54 cases of spontaneous miscarriage or missed abortion (15.5%). This is within the range of miscarriage rate in the general population of 11-22%, and therefore the risk of miscarriage does not seem to be increased after exposure to UPA during early pregnancy or in the cycle of conception.

The data, although still limited, are reassuring. Although a risk for the foetus cannot be completely excluded, the available data are sufficient to conclude that the risk of exposure of ellaOne is likely to be low. Further, during the first two weeks after conception, and before the expected date of menses, the developing embryo is not susceptible to teratogenesis.

Widening access to the non-prescription setting

As was also indicated in the outcome of the Article 31 Referral for emergency contraceptives, it is essential that emergency contraception is taken as soon as possible after unprotected intercourse as the mechanism of action is inhibition or delay of ovulation. It is considered very unlikely that widening access to the non-prescription setting will increase the time from unprotected intercourse to the emergency contraception intake. Instead, the opposite is more likely that in case emergency contraception is readily available without a prescription that the time from unprotected intercourse to taking of the tablet will decrease, as the woman does not need to collect a receipt of her HCP first. Moreover, study HRA2914-557 showed a shift towards shorter delay between UPI and intake/delivery observed for the non-prescription setting compared to the prescription setting. Further, the data of the study in adolescents HRA2914-515 are also considered relevant for this application, because adolescents will have easier access to ellaOne in a non-prescription setting. Based on this study it was shown that the efficacy and safety profile in adolescents is similar to women above 18 years of age. Lastly, in a non-prescription setting it could easier occur that women take ellaOne more than once in the same menstrual cycle. It is therefore important to have data on repeated administration regarding safety. Study HRA2914-554 showed that repeated administration in the same cycle is safe, and consequently the warning in section 4.4 of the SmPC that repeated administration within the same menstrual cycle was not advisable, as it was not investigated, was removed.

Contraindication pregnancy

The CHMP agrees with the removal of the contraindication ‘pregnancy’ for the following reasons:

- The update of data on exposure during pregnancy does not show an increased risk for miscarriage nor major malformations in comparison to the rate in the general population.
- Based on the mechanism of action of ulipristal there is no reason for concern regarding teratogenicity on scientific grounds.
- When including ‘pregnancy’ as a contraindication, ulipristal will in clinical practice be perceived as a harmful drug to the foetus and this will introduce the question whether an abortion should be performed after exposure during pregnancy.
- There appears to be no off-label use with the intent to terminate an existing pregnancy for this product.

Thus, in accordance with the relevant CHMP guideline (EMEA/CHMP/203927/2005) and in view of the experience with other EC products, pregnancy does not need to be a contraindication.

Benefit risk of ellaOne as a non-prescription product in young adolescents and adults

As efficacy of emergency contraception is based on inhibiting or delaying ovulation, emergency contraception is the most effective when taken as soon as possible after unprotected intercourse. Several studies have shown that intake of emergency contraception after UPI is sooner in a non-prescription setting than in a prescription setting.

The CHMP agreed with the MAH that the benefit risk balance of unrestricted access to emergency contraceptives on a non-prescription status is favourable in women of all ages, and that there is no scientific reason to impose an age restriction.

It is clinically documented that the efficacy and safety of ellaOne in postmenarcheal girls is similar to the efficacy and safety in the adult population. The observed pregnancy rate in postmenarcheal girls in study HRA2914-515 was 7 out of 464 subjects, i.e. 1.5%. This observed pregnancy rate is in accordance with the pregnancy rate in adult women present in the SmPC of ellaOne, i.e. 1.36%. Further, there were no clinically relevant differences between subjects under 18 years old and subjects aged 18 years and older in the occurrence of TEAEs.

Moreover, the MAH referred to the already existing experience with levonorgestrel-EC pharmacy programs in place in several EU countries and to their intention to liaise and collaborate with national pharmacy organisations and/or pharmacy postgraduate training providers, to consider how best to support pharmacists in the supply of ellaOne without prescription in accordance with national policies, and especially in dispensing EC to young adolescents. This is supported by the CHMP.

The CHMP considered that the benefit risk of ellaOne as a non-prescription product in young adolescents and adults has been adequately discussed and documented by the MAH. It is agreed with the MAH that the benefit risk assessment of unrestricted access to emergency contraceptives on a non-prescription status is favourable in women of all ages.

Conclusion by the CHMP about the third criterion

In view of the above discussion, the CHMP considered that Criterion 3 of Article 71 of Directive 2001/83/EC and the European Commission Guideline “Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side effects of which require further investigation” does not apply to ellaOne.

Fourth criterion: Medicinal products normally prescribed by a doctor to be administered parenterally

This criterion is not applicable for ellaOne.

2.6. Risk management plan

The MAH has submitted a new version of RMP (version 13) as part of this variation.

2.7. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 13, the PRAC considered by consensus that the risk management system for ulipristal acetate (ellaOne) for the indication 'emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure' is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Effects on pregnancy maintenance/off label use • Risk of incomplete abortion and heavy bleeding • Effects on foetus and newborns • Risk of ectopic pregnancy • Concomitant use of CYP3A4 inducers • Liver effects • Delayed menstrual period >60 days / amenorrhea • Ovarian cysts
Missing information	• Effect of concomitant use of progestin-only contraception • Effect in patients with severe asthma treated by oral glucocorticoid • Effects in women with impaired liver function

The PRAC agreed.

Pharmacovigilance plans

Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
A Pregnancy Registry to Collect Clinical Follow-up Information and Outcomes of Pregnancies Resulting from ellaOne Failure or Pregnancies inadvertently exposed to ellaOne Web-based registry	To assess clinical follow-up and outcome of pregnancies resulting from ellaOne failure or pregnancies inadvertently exposed to ellaOne.	Effects on pregnancy maintenance / off-label use Risk of incomplete abortion and heavy bleeding Risk of ectopic pregnancy Effects on foetus and newborn	Started Start date: October 2009	Reports of the aggregate data in the Registry will be compiled and submitted to health authorities via PSURs.

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Category: 3				

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the study in the post-authorisation development plan is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Effect on pregnancy maintenance / Off-label use as an abortifacient	SPC and package leaflet Information in section 4.2 Warning in section 4.4 of the SPC Information in section 4.6	None
Risk of incomplete abortion and heavy bleeding	SPC and package leaflet Information in section 4.2 Warning in section 4.4 of the SPC	None
Effects on foetus and newborns	SPC and package leaflet Information in section 4.2 Warning in section 4.4 Information in sections 4.6 and 5.3	None
Risk of ectopic pregnancy	SPC and package leaflet Warning in section 4.4 of SPC	None
Effect of concomitant use of CYP3A4 inducers	SPC and package leaflet Warning in section 4.4 Information in section 4.5. Interactions about mechanism of interaction and consequences of concomitant use CYP3A4 inducers. Concomitant use is not recommended.	None
Liver effects	None proposed.	None
Delayed menstrual period > 60 days / amenorrhea	Information about possibility of delayed menstrual period in SPC, section 4.4.	None
Ovarian cysts	Listed in SPC, section 4.8.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Effect of concomitant use of progestin-only contraception	SPC and package leaflet A warning and information that concomitant use with emergency contraception containing levonorgestrel is not recommended are included in sections 4.4 and 4.5 of the SPC. Information about interaction with progestogen-only contraception, possibility of reduced action, and need for use of barrier method is included in section 4.5 of the SPC.	None
Effect in women with severe asthma treated by oral glucocorticoids	SPC and package leaflet A warning is included in section 4.4. of the SPC that use in women with severe asthma treated by oral glucocorticoids is not recommended.	None
Effect in women with impaired liver function	SPC and package leaflet Information is included in section 4.2. of the SPC that there are no studies about dosage adjustments in women with impaired liver function. The use is not recommended in women with severe hepatic impairment.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice without changes.

2.8. Changes to the Product Information

At the time of submission of the variation the MAH proposed changes to the Summary of Product Characteristics, Annex II, the labelling and Package Leaflet in line with a non-prescription setting. The MAH also proposed updates of SmPC sections 4.2, 4.4 and 5.1 based on Repeated use study (Protocol 091015-001/CSR HRA2914-554 - SmPC sections 4.4 and 5.1) and on interim data from the STEella study in post-menarcheal girls and adult women (Protocol 2914-010/ EUDRACT nr 2009-017771-21/ CSR HRA 2914-515 - SmPC sections 4.2 and 5.1). The Package Leaflet and Labelling were proposed to be updated accordingly.
Furthermore the MAH proposed this opportunity to bring the PI in line with the QRD template and to make some editorial changes.

During the procedure, the Final Study Report of the STEella study was submitted.

The CHMP also requested some amendments to the Product Information. The main amendments requested to the Product Information are described below.

Summary of Product Characteristics

Section 4.2 Posology and method of administration
The MAH proposed a change to section 4.2 in order to include any women of childbearing age including adolescents based on the results of study HRA2914-515. Section 5.1 is also impacted by this change. The CHMP agreed with this change.

Section 4.3 Contraindications
The MAH provided sufficient data to support the removal of the pregnancy contraindication. Sections 4.2, 4.3, 4.4 and 4.6 of the SmPC and the Package Leaflet are impacted by the removal of the

pregnancy contraindication.

Section 4.4 Special warnings and precautions for use

The CHMP did not agree to delete the current recommendation that concomitant use of ellaOne and emergency contraception containing levonorgestrel is not recommended. The MAH was requested to reinstate this recommendation in SmPC 4.4 as a separate sentence.

Section 4.6 Fertility, pregnancy and lactation

The following text has been proposed by the MAH and agreed by the CHMP for the pregnancy section.

Pregnancy may occasionally occur after ellaOne intake. Although no teratogenic potential has been observed, animal data are insufficient with regard to reproduction toxicity (see section 5.3). Limited human data regarding pregnancy exposure to ellaOne do not suggest any safety concern. Nevertheless it is important that any pregnancy in a woman who has taken ellaOne be reported to www.hra-pregnancy-registry.com. The purpose of this web-based registry is to collect safety information from women who have taken ellaOne during pregnancy or who become pregnant after ellaOne intake. All patient data collected will remain anonymous.

The addition of the reference to the pregnancy registry is supported by the CHMP as it will allow the collection of more pregnancy data in the non-prescription setting.

Section 4.8 Undesirable effects

The MAH proposed the following paragraph to be included in this section.

A pharmacodynamic study of 23 subjects showed that repeat administration of ellaOne (once every five or seven days during eight consecutive weeks) is well tolerated with a safety and bleeding profile similar to that observed for a single 30 mg dose.

The inclusion of this paragraph has been considered as not acceptable by the CHMP as this information is already present in section 4.8 on repeated administration in the same cycle in the paragraph above. In addition the statement that ellaOne was provided every five or seven days is deemed confusing, as ellaOne is only intended for occasional use. The MAH agreed with the removal of this paragraph.

Section 5.1 Pharmacodynamic properties

The addition of the following paragraph was considered confusing by the CHMP, as it provides information on repeated administration in a period of two months, whereas ellaOne should be used only for occasional use and this has been also clearly stated in section 4.4. The statement that ovulation occurs after 3 to 6 tablets after repeated administration in the majority of the cases is difficult to translate to an individual woman. For these reasons, the inclusion of the following paragraph in section 5.1 was not considered acceptable by the CHMP.

"When administered repeatedly (eight to ten 30-mg doses within a period of two months), ovulation occurs after 3 to 6 tablets in the majority of cases, ulipristal acetate is well tolerated with a safety profile similar to that established for a single 30 mg dose."

Section 5.3

The MAH proposed the following change to that section.

No teratogenic effects have been observed in reproduction toxicity studies.
~~Reproduction toxicity data are insufficient due to lack of human and animal pharmacokinetic data. Due to its mechanism of action, ulipristal acetate has an embryolethal effect in rats, rabbits (at repeated doses above 1 mg/kg) and in monkeys. The safety for a human embryo is unknown. At doses which were low enough to maintain gestation in the animal species, no teratogenic potential was observed.~~

As there are no new animal data regarding reproduction toxicity studies, the MAH was requested to keep the original text for this section.
Following this request, the MAH proposed an updated statement to which the CHMP agreed.

Labelling

A QRD review and QRD consultation on the labelling proposal for ellaOne in the context of the switch to non-prescription status have been performed. Some changes have been implemented to the labelling further to the QRD review.

The CHMP also agreed with the inclusion of the QR code in the outer packaging linking to the electronic version of the package leaflet.

Package Leaflet (PL)

The MAH proposed a revised package leaflet of ellaOne adapted to the non-prescription setting and has undertaken readability testing among representatives of the target population. The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

A section has been added at the end of the leaflet to provide general information on the female reproductive system and further details on aspects already addressed in section 1 of the package leaflet.

3. Overall conclusion and impact on the benefit / risk balance

In the current application the MAH proposed a change in the classification for supply of ellaOne from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription" in the EU. The MAH also proposed updates of SmPC sections 4.2, 4.4 and 5.1 based on Repeated-use study (HRA2914-554) and on the STEella study in postmenarcheal girls and adult women (HRA 2914-515).

The CHMP agrees with the MAH that EC is the most effective when taken as soon as possible after unprotected intercourse, and that the accessibility to an EC in itself would be better with a 'non-prescription' status. Experience with levonorgestrel EC has shown that pharmacy access enables women to quickly use EC, and that women can appropriately use levonorgestrel EC without medical supervision.

The advantage of ellaOne compared to levonorgestrel is that ellaOne can be taken up to 120 hours after unprotected intercourse in contrast to levonorgestrel 1.5 mg, which is registered for up to 72 hours after unprotected intercourse. Moreover, a meta-analysis (HRA2914-541) on the results of the HRA2914-507 and HRA2914-513 studies show a lower pregnancy rate after ellaOne intake compared to levonorgestrel in the time window 0-72 hours.

EllaOne is an orally-active synthetic selective progesterone receptor modulator. EllaOne is able to delay follicular rupture (ovulation) for at least 5 days in a higher proportion of women than levonorgestrel when given in the late follicular phase, before LH surge and after LH surge but before LH peak. However, on the day of the LH peak ulipristal acetate, similar to levonorgestrel, cannot delay or inhibit ovulation any better than placebo.

The four criteria mentioned in Article 71 of Directive 2001/83/EC and the European Commission Guideline on changing the classification for the supply of a medicinal product for human use have been considered by the CHMP during the assessment of the variation.

1. Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision

Based on the fact that the safety of ellaOne has thoroughly been investigated in the studies at time of the initial marketing authorisation, that these data are now extended by a study on repeated administration (HRA2914-554; every 5 days and every 7 days) and a study in adolescents (HRA2914-515) and that the safety profile of ellaOne is comparable with levonorgestrel, the CHMP considered that criteria 1 does not apply to ellaOne.

2. Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health

Based on the fact that UPA is neither perceived or used as an abortifacient in the current setting, that animal data demonstrate that UPA is far less potent than mifepristone as an abortifacient and that abortion is legal in most EU countries, the CHMP considered that ellaOne is unlikely to be frequently and to a very wide extent used incorrectly in a non-prescription setting, and as a result are likely to present a direct or indirect danger to human health and that therefore criteria 2 does not apply to ellaOne.

3. Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof, the activity and/or side-effects of which require further investigation

Based on the fact that pharmacological activity and side effects of ellaOne have been characterized, that no significant safety findings have been identified and that the MAH provided sufficient reassurance on lack of negative effects to the foetus after uterine exposure to ulipristal (including teratogenicity) based on the updated non-clinical and clinical data now available, the CHMP considered that Criteria 3 does not apply.
Moreover, in accordance with the relevant CHMP guideline (EMEA/CHMP/203927/2005), the CHMP agreed with the removal of the pregnancy contraindication.
The CHMP also agreed that the benefit risk balance of ellaOne is positive in any women of child bearing age, including adolescents and therefore agreed on the proposed changes in section 4.2.

4. Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally (for injection)

The CHMP agreed that this criterion does not apply to ellaOne.

In conclusion, the CHMP considered that the four criteria mentioned in the European Commission Guideline on changing the classification for the supply of a medicinal product for human use do not apply to ellaOne and therefore the change in prescription status to not subject to medical prescription is approvable.

Furthermore, the Committee considers that this variation implements changes to the decision granting the marketing authorisation due to a significant public health concern on the following grounds:

This variation changes the legal status of the medicinal product, as discussed in section 2.5 above.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority of 21 out of 29 votes, the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation requested		Type
C.I.5.b	C.I.5.b - Change in the legal status of a medicinal product for centrally authorised products - All other legal status changes	II

Change in the classification for supply of ellaOne from "medicinal product subject to medical prescription" to "medicinal product not subject to medical prescription". An update of the Product information in line with a non-prescription setting was performed.
Updates of SmPC sections 4.2, 4.4 and 5.1 were also performed based on Repeated use study (HRA2914-554) and on the STEella study in postmenarcheal girls and adult women (HRA 2914-515).
Additionally, the contraindication “pregnancy” was removed based on available non-clinical and clinical data.
Updates to Annex II, labelling and package leaflet have been made accordingly.
Furthermore, changes were made to the PI to bring it in line with the current Agency/QRD template. In addition, editorial changes have been made in the Product Information. In addition, the MAH took the opportunity to update the list of local representatives for Bulgaria, Czech Republic, Poland, Romania, Hungary, Slovak Republic, Italy, Finland and Portugal in the Package Leaflet

Divergent positions to the majority recommendation for this variation have been expressed and are appended to the final opinion adopted for this procedure. Divergent positions are presented in Appendix 1 and 2.

The final AR has been revised and further adopted during written procedure on the 4th December 2014. All the other documents, part of the opinion package, have not been changed as adopted during the CHMP on the 20th December 2014.

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by Laboratoire HRA Pharma, SA, taking into account the provisions of Article 74(a) of Directive 2001/83/EC, and considers, by a majority of 21 out of 29 votes, that the clinical trials submitted in support of the classification of ellaOne as ‘medicinal product not subject to medical prescription’ are significant.

Divergent positions to the majority recommendation for this variation have been expressed and are appended to the final opinion adopted for this procedure.

APPENDIX
DIVERGENT POSITIONS

Divergent position 1

The undersigned members of CHMP did not agree with the CHMP's opinion recommending that the Marketing Authorisation status should be varied for ellaOne.

The reasons for divergent opinion were as follows:

According to Art 71 (1) of Dir 2001/83 EC medicinal products shall be subject to medical prescription where they:

…

— contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or

…

This third criterion applies for ulipristal acetate (UPA in emergency contraception (EC) because

- There is insufficient data to draw firm conclusions on fetotoxicity and teratogenicity of UPA in humans and therefore further investigations are required. Since an OTC setting is likely to lead to a more wide-spread use of UPA without proper counseling, this is of concern.
    - Until the data lock point of 1 August 2014, 568 cases of pregnancy following UPA intake have been reported. However, information on the outcome is available in 336 cases, including 56 live births (from 54 pregnancies), only. Of note, information on only 6 healthy babies (from 5 pregnancies) where UPA exposure occurred at the time of confirmed pre-existing pregnancy is available. Therefore, the number of exposed pregnancy outcomes/live births currently available is not considered sufficient to support a non-prescription status. Likewise, the time since marketing authorization of UPA is too short to firmly exclude long- term effects on children born after UPA exposure.
    - Of the 232 induced abortions, 134 "normal appearing" embryos/ fetuses were documented on ultrasound at the time of induced abortion. Usually, induced abortions are performed in early pregnancy. At that early stage, no evidence on embryofetal toxicity can be provided. Therefore, it cannot be concluded that all these pregnancies would have led to the birth of healthy babies.
    - The rate of malformations was indicated to be 1.4% based on 5/349 pregnancies and thus below the established rate of 3% in the general population (WHO, 2012). However the number of pregnancies with known outcome is 344 since 5 "normal appearing pregnancies" are still ongoing. Six newborns/fetuses with abnormalities or neonatal complications have been reported. It is agreed that it is unlikely that all of these cases are related to UPA. However, excluding the child with trisomy and another child with hypoxic complicated delivery, there remain 2 cases with severe malformations (optic nerve atrophy, Beckwith-Wiedemann Syndrome) out of 56 live births. Including the two abortions due to abnormalities (cardiac malformation without further information and one foetus with diaphragmatic aplasia and cardiopathy), this would result in a rate of malformation of 6.9% or 5.3% (if the child with optic nerve atrophy is excluded).
    - Although data in rats and monkeys, submitted with the initial marketing authorization application, did not indicate adverse effects of UPA when the embryo/foetus was exposed during early gestation, no conclusion for human safety could be drawn from these studies due to the small number of animals and low doses used.

- Potential misuse for intended abortion in an OTC setting is of concern. It cannot be concluded from the available data that UPA has no abortive potential.

  Available and interpretable clinical data are still very limited. UPA is chemically related to mifepristone and has caused abortion in animal studies. The minimum dose for the induction of abortion in humans is unknown. Although transferability to humans is unclear, results from nonclinical data do not show sufficiently that an effect of UPA as abortifacient can be excluded.

In conclusion, we believe that the third criterion of Art 71 (1) of Directive 2001/83 EG applies for UPA and therefore precludes a switch to OTC status.

…….	……
Harald Enzmann (Germany, BfArM)	Romaldas Mačiulaitis (Lithuania)
…….	……
Ivana Mikačić (Croatia)	Daniela Melchiorri (Italy)
…….	
Piotr Fiedor (Poland)	
…….	……
Agnes Gyurasics (Hungary)	Jan Mueller-Berghaus (Germany, PEI)

Divergent position 2

The undersigned member of CHMP did not agree with the CHMP's opinion recommending that the Marketing Authorisation status should be varied for ellaOne.

The reasons for divergent opinion is as follows:

According to Art 71 (1) of Dir 2001/83 EC medicinal products shall be subject to medical prescription where they:

…

— contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or

…

This third criterion applies for ulipristal acetate (UPA in emergency contraception (EC) because

- There is insufficient data to draw firm conclusions on fetotoxicity and teratogenicity of UPA in humans and therefore further investigations are required. Since an OTC setting is likely to lead to a more wide-spread use of UPA, this is of concern.
    - Until the data lock point of 1 August 2014, 568 cases of pregnancy following UPA intake have been reported. However, information on the outcome is available in 336 cases, including 56 live births (from 54 pregnancies), only. Of note, information on only 6 healthy babies (from 5 pregnancies) where UPA exposure occurred at the time of confirmed pre-existing pregnancy. Therefore, the number of exposed pregnancy outcomes/live births currently available is not considered sufficient to support a non-prescription status. Likewise, the time since marketing authorization of UPA is too short to firmly exclude long- term effects on children born after UPA exposure.
    - Of the 232 induced abortions, 134 "normal appearing" embryos/ fetuses were documented on ultrasound at the time of induced abortion. Usually, induced abortions are performed in early pregnancy. At that early stage, no evidence on embryofetal toxicity can be provided. Therefore, it cannot be concluded that all these pregnancies would have led to the birth of healthy babies.
    - The rate of malformations was indicated to be 1.4% based on 5/349 pregnancies and thus below the established rate of 3% in the general population (WHO, 2012). However the number of pregnancies with known outcome is 344 since 5 "normal appearing pregnancies" are still ongoing. Six newborns/fetuses with abnormalities or neonatal complications have been reported. It is agreed that it is unlikely that all of these cases are related to UPA. However, excluding the child with trisomy and another child with hypoxic complicated delivery, there remain 2 cases with severe malformations (optic nerve atrophy, Beckwith-Wiedemann Syndrome) out of 56 live births. Including the two abortions due to abnormalities (cardiac malformation without further information and one foetus with diaphragmatic aplasia and cardiopathy), this would result in a rate of malformation of 6.9% or 5.3% (if the child with optic nerve atrophy is excluded).
    - Although data in rats and monkeys, submitted with the initial marketing authorization application, did not indicate adverse effects of UPA when the embryo/foetus was exposed during early gestation, no conclusion for human safety could be drawn from these studies due to the small number of animals and low doses used.
- Potential misuse for intended abortion in an OTC setting is of concern. It cannot be concluded from the available data that UPA has no abortive potential. Available and

interpretable clinical data are still very limited. UPA is chemically related to mifepristone and has caused abortion in animal studies. The minimum dose for the induction of abortion in humans is unknown. Although transferability to humans is unclear, results from nonclinical data do not show sufficiently that an effect of UPA as abortifacient can be excluded.

In conclusion, the third criterion of Art 71 (1) of Directive 2001/83 EG applies for UPA and therefore precludes a switch to OTC status.

Furthermore the following reasons for being divergent are also presented as It cannot be concluded from the available data that UPA has no abortive potential, with this misuse in mind, the following concerns are listed:

1. Pregnancy normally cannot be considered a disease, and termination of pregnancy in a normal setting is not a therapeutic indication. It is a medical procedure only in distinct settings.

2. The medical termination of pregnancy involves the destruction and death of a human life. This falls under the definition contained in the *Guideline on the definition of a potential serious risk to public health*.

3. The benefit-risk of this product in the situations described is therefore negative.

4. This procedure is in direct conflict with the responsibility of medicine to protect and promote life.

5. The use of the product does not fit the definition of a Medicinal product "*Any substance or combination of substances presented as having properties for treating or preventing disease in human beings*;".

…….

John Joseph Borg (Malta)

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